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# Flow chemistry synthesis and sustainability assessment for choline chloride, a deep eutectic solvent constituent

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The continuous use of traditional solvents is not aligned with green chemistry principles, driving interest in natural deep eutectic solvents (NADES) as sustainable alternatives. This paper presents a two-step continuous-flow process for choline chloride production only from common biomass-derived precursors. Using water as the solvent, the method delivers 99% pure choline chloride and can generate NaCl as a byproduct depending on the base used. With a residence time of just 1 minute, the process reaches full conversion, achieving a 20-fold improvement in productivity compared to batch operation and enabling annual throughputs of up to half a ton per microcapillary. A comprehensive sustainability assessment highlights the advantages of using choline hydroxide (Ch-OH) as the base. When using Ch-OH, the process requires substantially less material and generates no byproducts, leading to a 51% reduction in energy demand and a 24% decrease in overall environmental impacts relative to NaOH. These benefits arise from lower input requirements, reduced wastewater generation, and higher process efficiency. Circularity performance also improves with Ch-OH, and life cycle assessment confirms that increased productivity outweighs the higher impacts associated with its production. Overall, the combined flow chemistry and Ch-OH strategy offers a highly efficient and more sustainable route to choline chloride.

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## Sustainability spotlight

This work addresses the need for cleaner and more resource-efficient production of deep eutectic solvents (DES) by introducing a high-yield, low-waste flow-chemistry route for choline chloride. The process delivers >99% yield in one minute, cuts energy use by 51%, eliminates side products, and doubles productivity through the use of choline hydroxide. Life cycle assessment confirms a 24% reduction in environmental impacts and a 15% increase in circularity. These advances contribute to more sustainable chemical manufacturing and align with UN SDGs 7 (affordable and clean energy), 9 (industry, innovation and infrastructure), and 12 (responsible consumption and production).

## 1. Introduction

The principles of green chemistry have driven not only chemistry itself, but also the development of eco-friendly technologies aimed at promoting sustainability and reducing the environmental impact of chemical processes. One of the key challenges is replacing solvents that contribute to environmental pollution with greener alternatives. This is especially important due to the toxicity and high volatility of many conventional solvents, which lead to harmful emissions of organic compounds into the atmosphere. In contrast, ionic

liquids (IL), which are molten salts at room temperature, have attracted significant attention for their unique physicochemical properties – such as hydrophilicity, viscosity, and density – as well as their potential applications in biocatalysis,<sup>1</sup> extraction processes,<sup>2,3</sup> and electrochemical systems. A notable advantage of ionic liquids is their tunability; their properties can be customized by selecting different combinations of cations and anions for specific purposes. However, their sustainability is often compromised due to poor biodegradability and biocompatibility, raising concerns about their disposal and potential accumulation in ecosystems.

As an eco-friendlier alternative to traditional solvents, deep eutectic solvents (DES) offer high versatility across a wide range of applications.<sup>4–7</sup> Due to their ability to form liquid phases at relatively low temperatures through the interaction between two or more solid or liquid components, DES result in eutectic mixtures with a melting point lower than that of each individual

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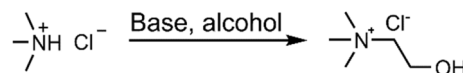


component. The first DES, described by Abbott *et al.*, was based on choline chloride as a hydrogen bond donor component in DES formulations.<sup>8</sup> Although it is not a DES itself, choline chloride is a common ingredient of DES formulations, for example, choline chloride–carboxylic acid dissolve lignin at 60 °C with recognized stability at 100–160 °C.<sup>9</sup> Choline chloride can be used either in human liver disorders or as a constituent in animal feeds.<sup>10</sup> Industrially, it is produced by the reaction of ethylene oxide (EtO), hydrogen chloride (HCl), and trimethylamine (TMA). Both EtO and HCl are hazardous gases. EtO is highly reactive, flammable, explosive, and associated with several health and environmental risks, meaning that conventional choline chloride production requires sophisticated equipment due to strict environmental and safety regulations.<sup>11</sup>

As a subclass of DES, natural deep eutectic solvents (NADES) are those composed of naturally occurring compounds.<sup>12</sup> Typical components of NADES can include sugars, organic acids, amino acids, and polyols, making NADES generally considered more sustainable due to their natural origin and biodegradability. However, the environmental impact of NADES can vary depending on the source and extraction process of their components, opening possibilities for their utilization in industries such as pharmaceuticals, green chemistry, and biotechnology. Due to their natural origin, NADES can also be produced from bio-based waste materials coming from (i) agriculture, *i.e.* husks, shells, and stems; (ii) food waste, *i.e.* fruit peels; (iii) industrial waste, *i.e.* glycerol from biodiesel; or (iv) biodegradable polymers, *i.e.* polylactic acid or polyhydroxyalkanoates, which can be broken down to yield NADES precursors. One of the compounds produced during the decomposition of organic matter, including plants, animals and animal waste is trimethylamine hydrochloride (TMAHCl), the hydrochloride salt of TMA.<sup>13</sup> TMAHCl is commonly used as a reagent in organic synthesis and as a precursor to produce quaternary ammonium compounds. It is also employed in biochemical research and as a stabilizer for certain polymers.

In this work, the use of TMAHCl as a precursor of choline chloride is proposed as a simple, sustainable, and safe pathway for the synthesis of choline chloride as potential scaled production of NADES (Scheme 1). The synthesis is enabled by the use of flow chemistry in continuous fashion, which enables to carry out reactions under extreme conditions in a safer manner compared to traditional batch methods.<sup>14–16</sup> This approach offers several advantages over traditional batch reactions, including improved safety, better control of reaction parameters, increased efficiency, the ability to conduct reactions that are not feasible or practical in batch mode due to reduced volumes, high mass and energy transfer and scale-up potential.<sup>17</sup> Additionally, flow chemistry prevent the loss of gas intermediates, namely TMA in this case, since all components are confined in the coil and can be dissolved in the liquid phase when the system operates under pressure.

The use of 2-chloroethanol (2ClEtOH) in the synthesis pathway is justified by the recent advances on C<sub>2</sub> platform chemicals, including ethylene, ethanol, and related intermediates such as 2ClEtOH, which can be fully derived from biomass



Scheme 1 General chemical pathway for choline chloride production proposed in this paper.

with documented environmental benefits.<sup>18</sup> 2ClEtOH can be credibly classified as a biomass-derived intermediate because all key precursors in its conventional production routes, namely ethanol, ethylene, and ethylene glycol, are currently available from bio-based feedstocks with demonstrated environmental advantages over petrochemical alternatives. Additionally, 2ClEtOH is manufactured at industrial scale, also using emerging electrocatalytic methods which enable the direct oxidative chlorination of ethylene to 2-chloroethanol under mild conditions.<sup>19</sup> When produced from bio-ethylene, the organic carbon content of 2ClEtOH is effectively biogenic.

The environmental compatibility of the process is herein evaluated under optimal operating conditions using a comprehensive multi-criteria holistic sustainability assessment, which include green chemistry metrics, circularity assessment, and a life cycle assessment (LCA).<sup>20</sup> While green chemistry metrics offer insights into the reaction in a pure chemical view, LCA delves into environmental impacts of the entire material chain from raw materials to process emissions, including energy flows. Circular economy globalizes all including also the mass flows of materials due to final disposal of components, focusing on reuse, reduce and recycle postulates, from cradle to cradle for an optimal and intense use of resources up to real exhaustion. In addition to a traditional holistic sustainability assessment, this study includes environmental risk assessment (ERA) to provide objective metrics. Unlike LCA, which evaluates broader environmental impacts across a product's entire life cycle, ERA focuses on the risk caused by chemical substances or emissions to human health and ecosystems based on the probability and magnitude of exposure and effects.<sup>21</sup> Combining metrics from these two approaches presents challenges.<sup>22</sup> However, combining ERA and LCA outputs by comparing toxicity levels from ERA with lifecycle emissions data from LCA, enhances the depth of the sustainability assessment providing a more comprehensive view of environmental trade-offs.<sup>22</sup>

## 2. Methodology

### 2.1. Chemical pathway

The mechanistic conversion of TMAHCl into choline chloride (Ch-Cl) proceeds through a Brønsted–Lowry deprotonation that generates TMA as the reactive nucleophile. Because TMAHCl is a quaternary ammonium salt, freeing TMA requires a base strong enough to shift the acid–base equilibrium toward the unprotonated amine. Two bases were evaluated to this aim: sodium hydroxide as a usual, inexpensive and strong base, and choline hydroxide (Ch-OH), which has been noted in the literature for catalytic activity.<sup>23</sup> By using Ch-OH the route herewith presented can be taken as potentially complementary, as Ch-OH



can be produced from ethylene oxide, trimethylamine, and water, in a process which does not generate chloride-containing byproducts, such as NaCl. This contrasts with conventional routes based on hydrochloric acid or alkali chlorides, where salt waste represents a significant environmental and operational burden. The Ch-OH pathway offers environmental advantages: (i) it eliminates inorganic chloride waste streams, (ii) operates in aqueous media with manageable exothermicity under continuous conditions, and (iii) produces a relatively clean hydroxide phase (40–50% concentration) alongside recyclable organic fractions, minimizing salt impurities. From a systems perspective, coupling the ethylene oxide-based choline hydroxide synthesis with choline chloride production can be envisioned as a closed-loop or cascade process, where the autocatalytic behavior of choline hydroxide facilitates choline chloride formation without introducing extraneous acidic reagents, while preserving the logical flow of material value.

The chemical mechanism involving sodium hydroxide is illustrated in Fig. 1. When using NaOH, it abstracts the proton from TMAH<sup>+</sup> to produce TMA but simultaneously generates NaCl as an unavoidable inorganic byproduct. The resulting TMA performs an S<sub>N</sub>2 substitution on 2ClEtOH, forming choline chloride.

When using Ch-OH, the deprotonation mechanism is analogous but avoids inorganic salt production because the conjugate acid formed is a choline cation rather than a metal salt, Fig. 2. Both organic cations share chloride as their counterion, leading to a cleaner reaction profile. TMA again reacts *via* S<sub>N</sub>2 with 2ClEtOH to yield Ch-Cl. Consequently, the use of Ch-OH enables the formation of two equivalents of Ch-Cl per equivalent of TMAHCl, limited only by the acid–base equilibrium and the efficiency of the substitution step. Whilst the strength of NaOH is higher (pK<sub>a</sub> = 15.7, 25 °C) than Ch-OH (pK<sub>a</sub> = 13.9, 25 °C), using NaOH results in a lower yield of choline chloride due to stoichiometry, along with higher waste production from NaCl formation. Nonetheless, the use of Ch-OH might report additional impacts potentially higher than the production of NaOH, as described below.<sup>24</sup>

## 2.2. Experimental

**2.2.1. Batch experiments.** In a batch screening, TMAHCl solutions and 2ClEtOH were premixed in a closed top cap with septa, stirring at 700 rpm. After preheating for 2 min, the base was added to initiate the reaction, *via* a needle and syringe,

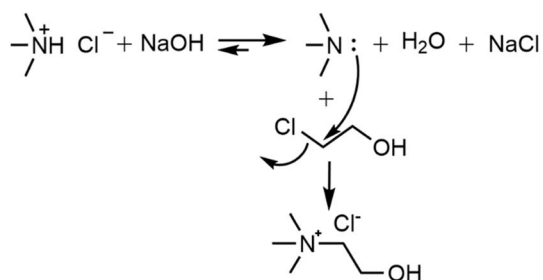


Fig. 1 Mechanistic pathway for the synthesis of choline chloride using NaOH as base.

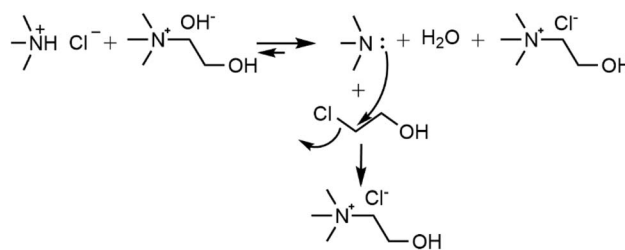


Fig. 2 Mechanistic pathway for the synthesis of choline chloride using Ch-OH as base.

stopping the reaction for each reaction time over ice. A minimum of 5 replicates of each experiment ensured reproducibility.

**2.2.2. Continuous flow experiments.** The flowchart of the engineering of the process is outlined in Fig. 3, illustrating the simplicity of the process. Polyfluoroalkyl (PFA) tubing of 1/8 in. OD (3.2 mm) and 1.56 mm ID (IDEX) were used in the whole system. A piston pump A (Syrris FRX), equipped with pressure sensor, pumped a concentrated TMAHCl solution (3.52 M, Merk) in distilled water, with the corresponding flow rate according to the experiment: examples are given on Table 1. TMAHCl concentration was selected because it is close to its water solubility limit, which allowed productivity maximization while ensuring stable flow through the coils. This solution was mixed using a T-valve (IDEX) with the corresponding 99% pure 2ClEtOH (Sigma-Aldrich), which was pumped solvent-free using a piston pump B (Syrris FRX), also equipped with pressure sensor, at a flow rate of *e.g.* 0.31 mL min<sup>-1</sup> to maintain an optimal stoichiometric ratio of TMAHCl : 2ClEtOH of 1 : 1. The resulting solution was then directed to a 1 m long preheater, submerged in an oil bath (silicon oil M100 Carl Roth GmbH, IKA HBR4) operating at 110 °C.

At the outlet of the preheater, the former solution was mixed using a T-valve (IDEX) with either a 50% NaOH aqueous solution (Merk) or a 46 wt% Ch-OH aqueous solution (Sigma-Aldrich) respectively, which was pumped by a third pump C (Azure P4.1S, Knauer) equipped with ceramic head and pressure sensor, Fig. 3. The resulting homogeneous mixture was introduced to the main reactor, consisting of a 3 m long coil submerged in an oil bath, like the one used in the preheater, operating at 110 °C. A cooler followed at the reactor outlet, comprising 1 m of tubing submerged in thermostatic water bath operating within a range of 20–30 °C. At the end, a back-pressure regulator (BPR, IDEX) was installed downstream of the reactor to keep a defined system pressure, meaning the valve remained fully closed below this threshold and only opened to relieve flow once the internal line pressure exceeded 20 bar. By increasing the operating pressure, the BPR ensured all internal components remained in liquid phase. This pressure was experimentally determined to be 20 bar. The solution was then collected in a storage tank, from which it was pumped to a mini spray dryer B-290 (Buchi) using a peristaltic pump to obtain a mixture of pure choline chloride and NaCl when operating with NaOH. The inlet spray drier temperature was set to 180 °C while 114 °C was the temperature in the outlet, with 40 mm



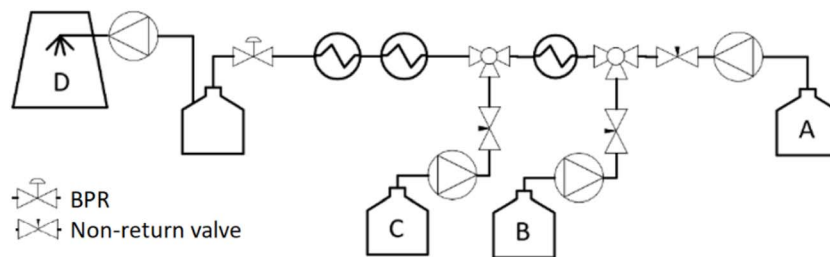


Fig. 3 Flowchart for choline chloride production from trimethylamine hydrochloride. (A = TMAHCl solution, B = 2ClEtOH, C = base solution, and D = spray drier).

Table 1 Examples of continuous flow experiment design including flow rates distribution

	Residence time (min)	Total flow (ml min <sup>-1</sup> )	<i>F</i> (ml min <sup>-1</sup> )		
			TMAHCl	NaOH	2ClEtOH
Continuous flow with NaOH	5	0.38	0.27	0.05	0.06
	2	0.94	0.66	0.12	0.16
	1	1.89	1.33	0.25	0.31
	0.67	2.82	1.98	0.37	0.47
	0.34	5.55	3.91	0.72	0.92
Continuous flow with Ch-OH	5	0.38	0.18	0.16	0.04
	2	0.94	0.45	0.39	0.11
	1	1.89	0.90	0.78	0.21
	0.67	2.82	1.34	1.16	0.32
	0.34	5.55	2.64	2.28	0.62

nebulization and full ventilation. In a subsequent discontinuous operation, NaCl was separated using ethanol absolute. Choline chloride was obtained by lyophilization under vacuum (discontinuous, Telstar LyoQuest), previously freezing at  $-80\text{ }^{\circ}\text{C}$  during 24 hours, when operating with Ch-OH. At least 5 replicates of each experiment ensured reproducibility.

Since both 2ClEtOH and the intermediate TMA are more volatile than water, ensuring complete removal of water and achieving stringent dryness specifications for the final Ch-Cl compound provided an assurance that residual 2ClEtOH and TMA remained well below relevant safety thresholds, confirming the final compound meets regulatory safety standards.

**2.2.3. NMR analysis.** <sup>1</sup>H-NMR spectroscopy was employed to monitor the reaction pathway and to characterize the final compound. Trace amounts of 2ClEtOH were not expected to be present in the final product due to the purification process and subsequent solvent evaporation. <sup>1</sup>H-NMR spectra were collected on a Varian AS400 spectrometer operating at 400 MHz. Approximately 10 mg of each sample was dissolved in 0.6 mL of deuterium oxide (D<sub>2</sub>O) and transferred into 5 mm NMR tubes. Maleic acid was used as the internal standard. The acquisition parameters included: spectral width 20 ppm, recycle delay 30 s, number of scans 128, acquisition time 8.7 s, and a 90° pulse angle experiments were conducted at 22 °C. Always relaxation delay was adjusted to match the longest *T*<sub>1</sub> in the sample for absolute quantitation. All spectra were Fourier transformed and processed and baseline correction was applied across the full spectral range.

### 2.3. Life cycle assessment

The sustainability of producing 1 kg of choline chloride, considered as the functional unit, was evaluated to compare the environmental impacts of two different chemical bases. A comprehensive LCA was conducted to evaluate the cradle-to-factory gate environmental performance of the process using Ch-OH, in comparison to the conventional process using NaOH. Impact categories were quantified using Ecoinvent 3.9.1 database, included in Sphera LCA for Experts software, version 10.7.0.183. The impact categories were selected according to recent life-cycle environmental references in chemicals production:<sup>25</sup> acidification (AP), global warming potential (GWP), ecotoxicity freshwater (ET), freshwater (EPw) and terrestrial (EPt) eutrophication, human toxicity cancer (HTc) and non-cancer (HTnc), Ionizing irradiation (Irr), particulate matter (PM), photochemical ozone formation (Ph), as well as resource use fossils (CED).

### 2.4. Circularity assessment

A circularity assessment is a tool to quantify the degree of resources usage up to exhaustion and minimize waste generation. This study follows the Ellen MacArthur Foundation (EMAF) methodology, which includes metrics like Material Circularity Indicator (MCI), ranging from 0 (fully linear, no circularity) to 1 (fully circular).<sup>26</sup> The EMAF completed its MCI with environmental indicators such as water and energy consumption or greenhouse gas emissions to add a sustainable



component when assessing the inherent circularity of materials.<sup>27</sup>

### 2.5. Green chemistry metrics

Green chemistry metrics were used to evaluate and quantify the environmental impact and sustainability of chemical processes. The methodology proposed by Roschangar was used to calculate the green chemistry metrics for the two proposed scenarios.<sup>28</sup> Green chemistry metrics provide an opportunity to evaluate chemical processes relative to green chemistry principles, enabling the strategic analysis of measures of relative process waste, manufacturing time and cost efficiency.<sup>29</sup>

### 2.6. Environmental risk assessment

Translating the potential environmental impacts identified in the LCA into potential risks using ERA methodology involves selecting key impact categories from the LCA that are relevant to ERA: such as ecotoxicity and human toxicity.

## 3. Results and discussion

### 3.1. Choline chloride synthesis

Before transferring the reaction to continuous flow, preliminary batch-screening experiments with NaOH were performed to evaluate the influence of temperature on substrate conversion. Under identical conditions conversions of 72% and 82% are obtained at 80 °C and 100 °C, respectively, whereas full

conversion is achieved at 110 °C after 20 min reaction time in batch with NaOH. These results justify the selection of 110 °C as the benchmark temperature for subsequent optimization studies. In parallel, the effect of the NaOH and alcohol molar ratio was examined to determine the minimum amount required to drive the reaction to completion, Fig. 4. The results show that a 1 : 1 molar ratio of NaOH and 1 : 1 molar ratio of alcohol are enough to achieve full conversion, with no additional improvements observed at higher ratios.

When comparing bases, results at 110 °C show an eminent higher speed reaction when operating with NaOH, Fig. 5. This can be initially attributed to the slightly higher strength of the base for the chlorine extraction in the first step, Fig. 1 and 2. The lower basicity of Ch-OH might lead to slower reaction in batch, achieving only 80% yield after 20 min. Nevertheless, the TMAHCl conversion is complete in both cases, indicating all raw material is transformed to TMA intermediate. An alternative explanation would consider enough the basicity of Ch-OH for proton extraction, while the NaCl production when using NaOH might made TMA less soluble in water, thereby increasing the reaction speed of 2ClEtOH addition. The explanation of yield difference relies consequently in two ways: first, the slow kinetic nature of the alcohol addition, as proton extraction performs much faster; second, the reaction is limited



Fig. 4 Reaction screening in batch reactors as described in this work.

Table 2 Mass balance of the reaction screening study of the reaction in batch, for each set of min. 5 replicates. (conversion refers to TMAHCl)

Base	Time, min →	Mass balance (%)			
		5	10	15	20
NaOH	Choline chloride	81 ± 0.92	98 ± 0.64	99 ± 0.62	99 ± 0.42
	2ClEtOH	11 ± 0.15	<0.1	<0.1	<0.1
	TMA	8 ± 0.21	2 ± 0.08	1 ± 0.02	1 ± 0.02
	Conversion	>99	>99	>99	>99
Ch-OH	Choline chloride	64 ± 1.91	78 ± 1.22	80 ± 0.93	80 ± 0.72
	2ClEtOH	20 ± 0.96	10 ± 0.44	8 ± 0.12	7 ± 0.08
	TMA	16 ± 0.62	11 ± 0.42	12 ± 0.37	12 ± 0.33
	Conversion	99 ± 0.82	99 ± 0.56	>99	>99

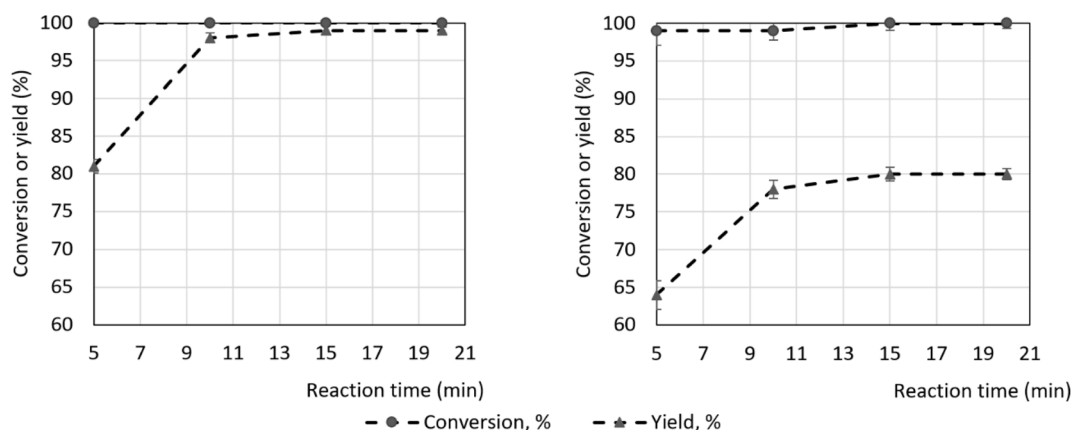


Fig. 5 Study of the reaction in batch, using either NaOH (left) or Ch-OH (right) as base.



by the gas–liquid mass transfer interaction in batch operation. Whilst the first refers to the nature of chemistry leading to more challenging improvement, the second can be overcome in continuous flow by pressurization, offering the chance for process intensification.

The results and the absence of side compounds were confirmed by  $^1\text{H-NMR}$  using  $\text{D}_2\text{O}$  as the solvent and maleic acid as an internal standard for quantification, which was performed considering the half of the final yield obtained due to the double choline chloride molar production when using Ch-OH. Based on this information, the mass balance was set accordingly, Table 2. While no relevant changes were observed between 15 and 20 min when operating with NaOH, the reaction was not complete when operating with Ch-OH in 20 min. In the latter, although there was full conversion of initial raw material, the remaining intermediate TMA and the presence of alcohol decreased the yield of the reaction towards choline chloride, concluding in an incomplete reaction.

When the experiments were performed in continuous flow, the results were different substantially, as the reaction was complete in just 1 min regardless of the base used, namely NaOH or Ch-OH respectively. Fig. 6 shows the yield *versus* time study performed in continuous flow when using NaOH as base, where the evolution of species can be followed achieving full conversion and high yield in just 1 min. In terms of productivity under lab scale conditions, since the process reaches >99% yield regardless of the base used, a production capacity of  $344 \text{ kg y}^{-1}$  is achieved when operating with NaOH and the double ( $688 \text{ kg y}^{-1}$ ) when using Ch-OH. Potential scaling up strategies in flow chemistry have been widely studied in the literature, demonstrating the capacity of this continuous production to be transferred to pilot and industrial scale.<sup>17</sup>

### 3.2. Choline chloride purification

The purification was aborbed using two approaches: choline chloride was purified using lyophilization (discontinuous, performed under vacuum previous freezing at  $-80 \text{ }^\circ\text{C}$ ) when using Ch-OH as base, while continuous spray drying was used for choline chloride purification when using NaOH as base. The synthesis setup was connected to a spray drier to get the final powder when operating with NaOH using a reservoir tank in between. To prevent accumulation, the flow rate of the peristaltic pump was adjusted according to the synthesis flow, Fig. 3. The inlet spray drier temperature was set to  $180 \text{ }^\circ\text{C}$  while  $114 \text{ }^\circ\text{C}$  was the temperature in the outlet, with 40 mm nebulization and full ventilation. Under these conditions, a powder containing a 70 : 30 weight ratio of choline chloride and NaCl was obtained with the payback of 7% mass losses of powder on the cyclone walls (suitable to be recovered during system cleaning with water), Fig. 7. While choline chloride and NaCl mixture could be sold as such, a further separation was performed using ethanol. The solubilities of choline chloride and NaCl on this solvent are 28 and  $0.65 \text{ mg mL}^{-1}$  respectively, 43 times higher, ensuring an efficient separation. The extraction was performed in batch using 3 : 1 weight ratio of ethanol in 3 sequential extractions, obtaining 83% efficiency (cumulating 60, 19 and 4% pure choline chloride respectively). The three production steps cumulated overall 77% yield, including >99% in the synthesis, 93% recovery in the spray dryer and 83% in the salt separation when operating with NaOH as base. The extracted salt containing also choline chloride is suitable to be recycled as such after ethanol evaporation. In the case of using lyophilization when using Ch-OH, the purification led to 78% efficiency, yielding also overall 77% yield.

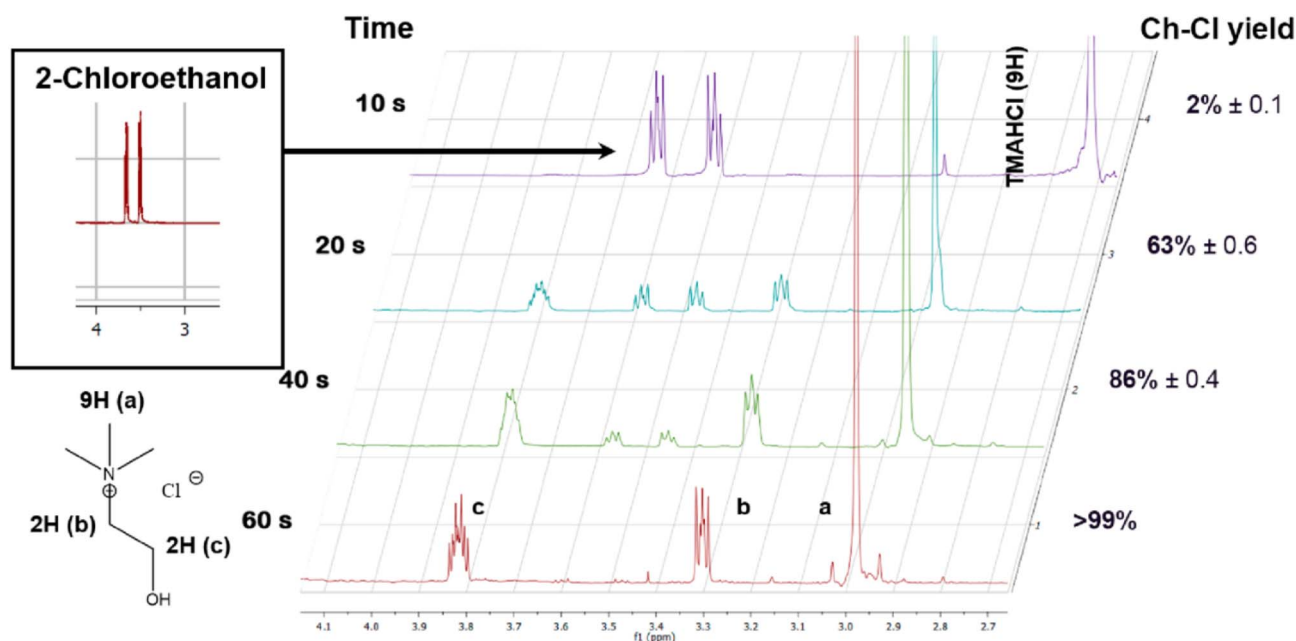


Fig. 6 Kinetic study of the synthesis of choline chloride (Ch-Cl) in continuous flow, using NaOH as base, based on results from min. five replicates.





Fig. 7 Continuous purification process of choline chloride obtained using NaOH as base.

### 3.3. Sustainability assessment

**3.3.1. Life cycle assessment.** As aforementioned, the sustainability of the process for producing 1 kg of choline chloride was investigated to compare the environment impacts of using two different chemical bases. Electricity from wind energy located in Spain is considered as case study. The life cycle inventory (LCI) for both processes is presented in Table 3. As most of chemicals involved are not included in the current version of impacts' database, similar compounds and former processes are modelled to estimate the environmental impacts of the raw materials, Fig. 8. For example, ammonia, NaOH, HCl and formaldehyde were used to quantify the production of TMAHCl, denoted as trimethylamine as raw material of the reactor.<sup>30</sup> This procedure is considered as more accurate than a simple substitution by similar compounds, ensuring the credibility and reproducibility of the results. Purification is not included in the LCA in this section, as the evaluation of optional purification procedures are evaluated separately in the corresponding subsection.

According to the LCA inventory, Table 3, environmental impacts were calculated using European environmental footprint (EF) 3.1 methodology, including 11 midpoint impact categories, Table 4. A normalized non-dimensional comparative factor for each category was calculated as the ratio of the corresponding impact when using Ch-OH, referred to the value when using NaOH. This ratio exceeds 1 when impacts increase with the use of Ch-OH, falls below 1 when impacts decrease, and equals 1 when there is no change.

For the process under assessment, this coefficient exhibits values below 1 in 9 over 11 categories, indicating lower impacts for choline chloride production using Ch-OH. Despite being more sustainable the production of NaOH than Ch-OH, the double molar yield per mol of initial TMAHCl reduces the global impacts of Ch-OH pathway when the production is normalized to 1 kg. Substantial reductions were observed in non-cancer toxicity (86%) and ionizing irradiation (68%), while key categories such as climate change (39%) and freshwater ecotoxicity (53%) exhibit slightly lower impact reductions. Interestingly, energy scores are reduced by 51%, mainly due to electrolytic processes used to obtain NaOH in addition to the productivity factor explained above. On the counterpart, the use of Ch-OH increases impacts regarding carcinogenic potential (12%) and a factor of  $\times 2.6$  the impacts on freshwater eutrophication (159%), which emerges as the key drawback of the use of Ch-OH. Yet, the overall sustainability coefficient, calculated as the average of the non-dimensional ratios scored 0.76, denoting a 24% decrease in environmental impacts when using Ch-OH instead of NaOH as the base.

Fig. 9 presents the relative contributions of individual reactants, products, and electricity consumption to the environmental impact profile. In addition to the absolute scores of the environmental impacts, their distribution is very different in both scenarios. While the base production accounts for 10–20% of the environmental impacts when using NaOH, Fig. 9a, these are increased up to 82% when operating with Ch-OH, Fig. 9b. This increase is balanced by reduction on the contribution TMAHCl and 2ClEtOH impacts, as lower amounts are required due to double molar efficiency. The production of NaCl as byproduct contributes average 10% to the environmental impacts when operating with NaOH, whilst this is not generated when using Ch-OH. Energy and water impacts have minor impact contributions, the latter caused by the short residence time in the heated reactor. Especially relevant is the contribution on EPw (82%) and HTC (42%), confirming that the high values on Table 4 are caused by Ch-OH production. Overall, the three main reactants share the average of the impacts by one third each, while these proportions are more unbalanced when operating with NaOH, leading to 42, 29 and 11% for TMAHCl, 2ClEtOH and NaOH respectively.

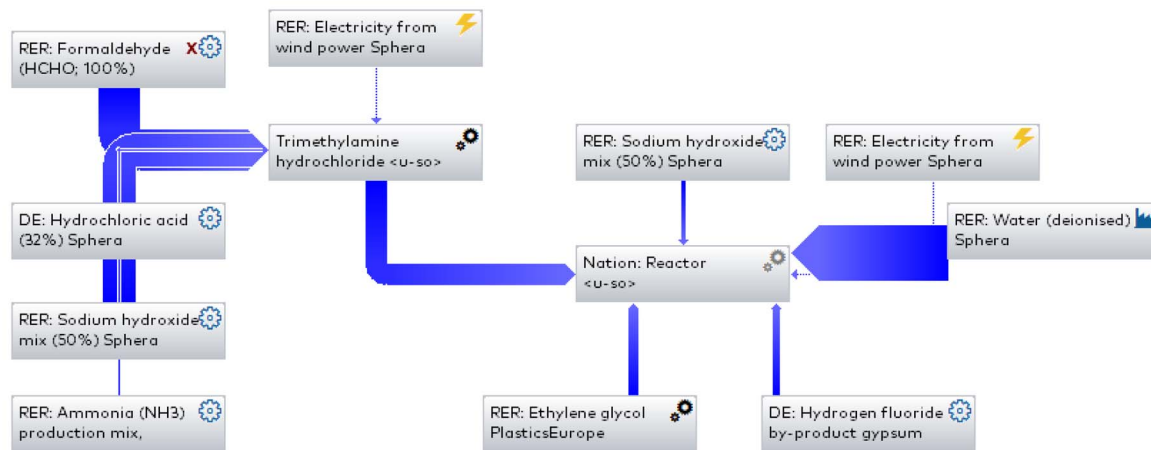
The comprehensive sustainability comparison between NaOH and Ch-OH-based processes reveals significant

Table 3 Life cycle inventory (LCI) for 1 kg choline chloride production either using NaOH or Ch-OH as base

Inputs	Base: NaOH		Base: Ch-OH		Ecoinvent inputs
TMAHCl	682.6	g kg <sup>-1</sup> choline chloride	341.3	g kg <sup>-1</sup> choline chloride	Calculated as a result of a subprocess, Fig. 8a and b
2ClEtOH	567.6	g kg <sup>-1</sup> choline chloride	284.0	g kg <sup>-1</sup> choline chloride	Calculated as a result of a subprocess, Fig. 8a and b
NaOH	190.7	g kg <sup>-1</sup> choline chloride	—	g kg <sup>-1</sup> choline chloride	Sodium hydroxide (50%)
Ch-OH (40% solution)	—	g kg <sup>-1</sup> choline chloride	434.0	g kg <sup>-1</sup> choline chloride	Calculated because of a subprocess, Fig. 8b
Distilled water	1764	g kg <sup>-1</sup> choline chloride	1196	g kg <sup>-1</sup> choline chloride	Deionized water
Energy	6.2	MJ kg <sup>-1</sup> choline chloride	6.2	MJ kg <sup>-1</sup> choline chloride	Electricity from wind power



a)



b)

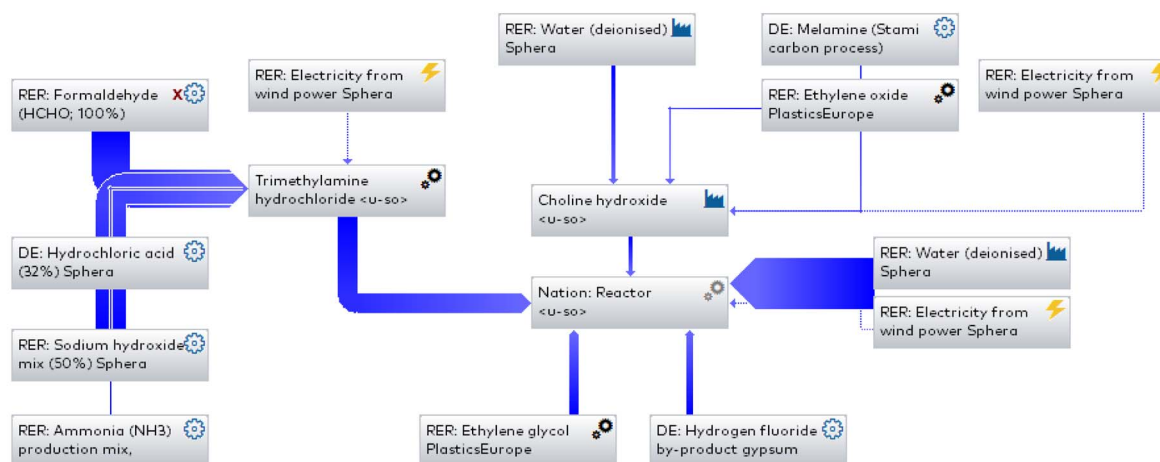


Fig. 8 Life cycle assessment for choline chloride production using either NaOH (a) or Ch-OH (b) as base.

Table 4 Environmental impact categories under study for 1 kg choline chloride production either using NaOH or Ch-OH as base, and normalized comparison

Impact category	Units	Symbols	NaOH	Ch-OH	Ch-OH/NaOH
Acidification	Mole of H <sup>+</sup> eq.	AP	$1.34 \times 10^{-2}$	$1.06 \times 10^{-2}$	0.80
Climate change	kg CO <sub>2</sub> eq.	GWP	$3.60 \times 10^0$	$2.18 \times 10^0$	0.61
Ecotoxicity, freshwater	CTUe	ET	$4.67 \times 10^1$	$2.21 \times 10^1$	0.47
Eutrophication, freshwater	kg P eq.	EPw	$1.66 \times 10^{-5}$	$4.31 \times 10^{-5}$	2.59
Eutrophication, terrestrial	mole of N eq.	Ept	$3.02 \times 10^{-2}$	$1.65 \times 10^{-2}$	0.55
Human toxicity, cancer	CTUh	HTc	$1.55 \times 10^{-9}$	$1.74 \times 10^{-9}$	1.12
Human toxicity, non-cancer	CTUh	HTnc	$8.81 \times 10^{-8}$	$1.26 \times 10^{-8}$	0.14
Ionizing radiation, human health	kBq U <sub>235</sub> eq.	Irh	$3.91 \times 10^{-1}$	$1.23 \times 10^{-1}$	0.32
Particulate matter	Disease incidences	PM	$1.51 \times 10^{-7}$	$1.03 \times 10^{-7}$	0.68
Photochemical ozone formation	kg NMVOC eq.	Ph	$8.43 \times 10^{-3}$	$5.39 \times 10^{-3}$	0.64
Resource use, fossils	MJ	CED	$1.09 \times 10^2$	$5.30 \times 10^1$	0.49

advantages across multiple metrics (Table 5). When evaluating green chemistry parameters, circularity indicators, and life cycle impacts, the Ch-OH pathway demonstrates superior environmental performance despite initial stoichiometric considerations. Notably, the Ch-OH process achieves 75% better

performance in green chemistry metrics compared to NaOH, primarily due to eliminated NaCl byproduct generation and reduced material inputs. This is reflected in its atom economy (54% compared with 44%) and remarkably low E-factor (0.1 compared with 0.8 kg waste/kg product). The material



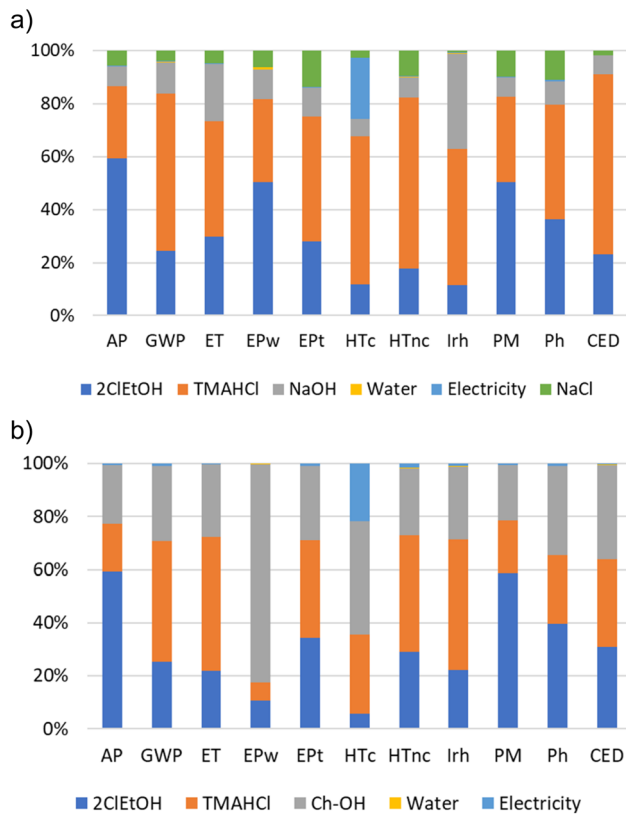


Fig. 9 Life cycle assessment impacts distribution when operating with NaOH (a) or Ch-OH (b) as base. (acidification, AP; global warming potential, GWP; ecotoxicity freshwater, ET; eutrophication potential freshwater, EPw; eutrophication potential terrestrial, EPT; human toxicity cancer, HTc; non-cancer, HTnc; ionizing irradiation, Irh; particulate matter, PM; photochemical ozone formation, Ph; resource use fossils, CED).

circularity indicator (MCI) reaches 0.67 for Ch-OH, representing a 10% improvement over NaOH's 0.61, driven by better resource utilization efficiency.<sup>31</sup>

Potential applications of these findings in the context of state-of-the-art research are summarized in Table 5. One potential case involves DES production by combining Ch-Cl with urea. Although synthesized through a semi-continuous process and demonstrating overall lower environmental impacts compared to conventional organic solvents, its environmental advantage does not extend to simpler alcohols such as methanol and ethanol. However, the present study offers contributions in process simplification and the use of renewable raw materials. Similar improvements can be considered when combining Ch-Cl with formic acid in the pretreatment of microalgae. Additionally, the greener synthesis route and process enhancements demonstrated in this study may improve the environmental performance of applications that have historically shown less favorable profiles, such as the use of Ch-Cl-based DES in the extraction of phenolic compounds.

In the field of carbon dioxide capture, DES have been reported to exhibit significantly lower impacts in categories such as EP, ET, and HT. These environmental advantages have previously been offset by the complexity and resource intensity

of DES synthesis. This study addresses those challenges through simplified process design and the use of waste-derived raw materials, thereby enhancing the overall sustainability of these solvents. Furthermore, the biomass-based processing of choline chloride for IL production can demonstrate considerable improvements in terms of sustainability.

In our case, while the LCA shows higher absolute impacts for Ch-OH production (12.3 vs. 8.7 kg CO<sub>2</sub>-eq kg<sup>-1</sup>), its doubled productivity effectively halves environmental burdens per functional unit. This trade-off highlights the importance of considering both process efficiency and upstream impacts when selecting sustainable pathways.<sup>39</sup>

**3.3.1.1 Purification process.** The purification process was analyzed separately due to its substantial contribution to the overall energy demand of the proposed sustainable route and because Ch-Cl can also be marketed water-dissolved. Two energy-intensive alternative unit operations, lyophilization (freeze-drying) and spray drying, were evaluated, as both are technically feasible for the final product isolation. For lyophilization, the total energy demand of a 24-hour vacuum freeze-drying cycle was estimated based on equipment operational characteristics rather than nominal power ratings. According to manufacturer data, the maximum electrical power of the equipment is 495 W at an ambient temperature of 35 °C, representing peak load conditions that do not occur continuously. Freeze-drying was modeled as a three-phase process comprising (i) initial cooling and sample freezing (2–4 h, 400–500 W), (ii) primary drying (sublimation) (10–15 h, 200–300 W), and (iii) secondary drying and system maintenance (4–8 h, 100–200 W). Using average power values representative of each phase and corresponding operating times, the total energy demand was calculated as:  $(3 \times 0.450) + (13 \times 0.250) + (8 \times 0.150) = 5.8$  kWh. A similar estimation approach was applied to the mini spray drier. Although the manufacturer specifies a maximum electrical power of 2.9 kW, actual energy use during standard operation is notably lower due to adaptive thermal control and part-load efficiency. An average consumption rate of approximately 2.0 kWh h<sup>-1</sup> was used, resulting in a total energy requirement of approximately 34 kWh per functional unit. The source of this energy significantly influences the environmental profile of the purification step. Consequently, five representative energy supply options were considered on Table 6: low-voltage electricity mix, natural gas combustion, nuclear-based electricity, wind energy, and photovoltaic electricity, while comparing for both purification procedures.

A comparative analysis between Tables 4 and 6 allows for the classification of environmental impact categories into three groups according to their relative contribution to the overall environmental burden. Categories such as EPT, HTnc, Ih, Ph, and CED exhibit negligible influence on the aggregated environmental results, indicating that their contribution remains marginal across the assessed system boundaries. In contrast, energy-related processes exert a dominant influence on EPw, HTc, and PM, revealing a strong dependency of these indicators on energy inputs and associated emissions. A third group, comprising AP, GWP, and ET, demonstrates an intermediate effect, representing categories that contribute moderately to the



Table 5 LCA for DES/ionic liquid solvents applications

DES/Ionic liquid	Synthesis method/others	LCA	Ref.
Choline chloride/urea DES (reline)	Synthesis using semi-continuous process	- The DES had a lower environmental impact than dichloromethane and ethyl acetate for almost all the considered indicators, but it was overcome by methanol and ethanol, whose manufacturing was more environmentally friendly - The feedstocks and the synthesis of the two components, Ch-Cl and U, account for the largest part of the burden on the seven indicators	32
Choline chloride/formic acid DES	DES for microalgae pretreatment	- Although the addition of DES during hydrothermal disintegration (HTD) increased the energy output by 36.3%, the net energy ratio (NER) increased from 0.65 to 0.83 due to the larger increase in energy input - DES synthesis was found to consume a lot of energy, which accounted for 45.9% of the total energy input - The addition of DES also increased the net GHG emissions from $-25.53 \text{ g CO}_2\text{-eq MJ}^{-1}$ to $26.04 \text{ g CO}_2\text{-eq MJ}^{-1}$	33
Choline chloride-based DES	Phenolic compounds extraction using DES	- The extraction process using DES leads to increasing environmental impacts when compared with ethanol. - This study used secondary data to perform the LCA; therefore, further research is needed to experimentally analyze a broader range of DES system ratios under optimal process conditions	34
Tetrabutylammonium bromide (TBAB) and decanoic acid (DEC)	CO <sub>2</sub> capture	- The CO <sub>2</sub> capture with TBAB-2DEC has significantly lower values in eutrophication potential (EP), freshwater aquatic ecotoxicity (FAE) and human toxicity (HT), especially in HT, demonstrating the advantage of less ecotoxicity of the DES. However, in terms of acidification potential (AP) and global warming potential (GWP), the TBAB-2DEC scenario shows higher environmental loads in comparison to MEA, which is due to the higher solvent flow, electrical energy, and cooling energy consumption	35
Choline chloride	Wood pretreatment	- LCA provides evidence that the DES one-step treatment introduces fewer environmental impacts (EI) than the traditional two-step method of wood pretreatment	36
[C6MIM][Cl] and [C6Py][Cl]	Cost and environmental LCA of the [C6MIM][Cl] synthesis and comparison to [C6Py][Cl].	- A reduction of 78% has been achieved concerning the cumulative energy demand (CED) - Reduction of the CED in contrast to the reduction of other impact categories (abiotic resource depletion potential, global warming potential, ozone depletion potential, acidification potential, eutrophication potential, photochemical ozone creation potential, human toxicity potential, freshwater aquatic ecotoxicity, marine aquatic ecotoxicity potential. And terrestrial ecotoxicity potential	37
[Bmim][Br]	Use of an ionic liquid ([Bmim] Br) in the production of acetylsalicylic acid	- The IL had larger environmental impacts than the organic solvent, particularly in the ecotoxicity impact categories	38

total environmental impact without being either dominant or insignificant. This pattern is followed by all energy sources considered, including green sources.

**3.3.2. Circularity assessment.** A circularity assessment is also investigated for this process framed in a circular economy context taking material flows extracted from the life cycle inventory (Table 3).<sup>40</sup> Assumptions for this assessment include (i) 20% losses during recycling water, and (ii) the utility factor of 1 as all scenarios might give the same performance, as commonly considered in chemical processes.<sup>41</sup> When using Ch-OH, due to the high yield of the reaction and the use of equimolar ratio of reactants, the only component suitable to be recycled is water, which it is collected considering 80%

efficiency. In contrast, whilst suitable to be used on secondary processes, NaCl is considered as waste when operating with NaOH, taking water recycling under the same conditions as with Ch-OH. Under these considerations, the circularity metrics of the process are defined and calculated on Table 7. The MCI is 10% higher when using Ch-OH, primarily due to reduced waste generation, as the recycling fraction remains similar in both cases. Differences in mass inputs (*M*) and virgin materials (*V*) reflect the different molar ratio used in each scenario. Sankey diagrams for the mass flow, shown in Fig. 10, further confirm that Ch-OH requires lower raw material demands and generates less waste to achieve the same productivity of choline chloride



Table 6 Environmental impacts derived from energy expenses in the purification step to produce 1 kg choline chloride either using NaOH (spray drying) or Ch-OH (lyophilization) routes

Paper	AP	GWP	ET	CED	EPw	Ept	HTc	HTtrc	Irth	PM	Ph	
	mol H <sup>+</sup>	kg CO <sub>2</sub>	CTUe	MJ	kg P	mol N	CTUh	CTUh	kBq U <sub>235</sub>	Disease i.	kg NMVOC	
Lyophilization	Electricity mix, low voltage	$3.02 \times 10^{-3}$	$3.78 \times 10^{-1}$	$8.15 \times 10^0$	$1.32 \times 10^0$	$1.27 \times 10^{-4}$	$1.22 \times 10^{-2}$	$1.22 \times 10^{-9}$	$3.19 \times 10^{-8}$	$2.41 \times 10^{-2}$	$4.19 \times 10^{-8}$	$2.74 \times 10^{-3}$
	Natural gas, 10 MW	$9.80 \times 10^{-3}$	$4.33 \times 10^0$	$2.27 \times 10^1$	$8.83 \times 10^1$	$3.99 \times 10^{-7}$	$3.03 \times 10^{-2}$	$3.03 \times 10^{-10}$	$9.46 \times 10^{-9}$	$-3.62 \times 10^{-3}$	$2.75 \times 10^{-8}$	$1.14 \times 10^{-2}$
	Nuclear, pressure water reactor	$2.95 \times 10^{-4}$	$4.24 \times 10^{-2}$	$1.23 \times 10^1$	$7.67 \times 10^1$	$2.61 \times 10^{-5}$	$8.46 \times 10^{-4}$	$1.35 \times 10^{-10}$	$2.10 \times 10^{-9}$	$4.17 \times 10^0$	$1.89 \times 10^{-8}$	$2.50 \times 10^{-4}$
	Wind, >3 MW turbine, onshore	$1.66 \times 10^{-3}$	$2.48 \times 10^{-1}$	$2.31 \times 10^1$	$2.72 \times 10^0$	$1.46 \times 10^{-4}$	$3.77 \times 10^{-3}$	$1.16 \times 10^{-9}$	$2.96 \times 10^{-9}$	$6.46 \times 10^{-3}$	$2.17 \times 10^{-8}$	$1.27 \times 10^{-3}$
Spray drying	Photovoltaic, 3kWp	$-1.71 \times 10^{-3}$	$7.71 \times 10^{-1}$	$5.27 \times 10^1$	$9.30 \times 10^0$	$3.63 \times 10^{-4}$	$1.03 \times 10^{-2}$	$1.72 \times 10^{-9}$	$5.51 \times 10^{-8}$	$3.01 \times 10^{-2}$	$4.74 \times 10^{-8}$	$3.06 \times 10^{-3}$
	Electricity mix, low voltage	$1.77 \times 10^{-2}$	$3.34 \times 10^0$	$2.21 \times 10^2$	$4.78 \times 10^1$	$7.71 \times 10^{-4}$	$7.44 \times 10^{-2}$	$7.13 \times 10^{-9}$	$1.87 \times 10^{-7}$	$1.41 \times 10^{-1}$	$2.46 \times 10^{-7}$	$1.60 \times 10^{-2}$
	Natural gas, 10 MW	$5.75 \times 10^{-2}$	$2.54 \times 10^1$	$1.33 \times 10^2$	$4.00 \times 10^2$	$5.18 \times 10^{-6}$	$2.34 \times 10^{-1}$	$1.78 \times 10^{-9}$	$5.54 \times 10^{-8}$	$-2.12 \times 10^{-2}$	$1.61 \times 10^{-7}$	$6.69 \times 10^{-2}$
	Nuclear, pressure water reactor	$1.73 \times 10^{-3}$	$2.48 \times 10^{-1}$	$7.23 \times 10^1$	$4.49 \times 10^2$	$1.53 \times 10^{-4}$	$4.96 \times 10^{-3}$	$7.93E-10$	$1.23 \times 10^{-8}$	$2.45 \times 10^1$	$1.11 \times 10^{-7}$	$1.46 \times 10^{-3}$
Wind, >3 MW turbine, onshore	$9.74 \times 10^{-3}$	$1.46 \times 10^0$	$1.35 \times 10^2$	$1.59 \times 10^1$	$8.57 \times 10^{-4}$	$2.21 \times 10^{-2}$	$6.78 \times 10^{-9}$	$1.74 \times 10^{-7}$	$3.79 \times 10^{-2}$	$1.27 \times 10^{-7}$	$7.43 \times 10^{-3}$	
Photovoltaic, 3 kWp	$-1.00 \times 10^{-2}$	$4.52 \times 10^0$	$3.09 \times 10^2$	$5.45 \times 10^1$	$2.13 \times 10^{-3}$	$6.04 \times 10^{-3}$	$1.01 \times 10^{-8}$	$3.23 \times 10^{-7}$	$1.77 \times 10^{-1}$	$2.78 \times 10^{-7}$	$1.80 \times 10^{-2}$	

demonstrating a higher process efficiency and simplicity compared to NaOH.

**3.3.3. Green chemistry metrics.** Green chemistry metrics are calculated for the two scenarios of the production process. These metrics, together with LCA and circularity metrics, collectively contribute to the sustainability assessment for the development of greener chemical processes environmentally compatible.<sup>12</sup> Whilst atom economy (AE) is favorable to the use of NaOH, as stoichiometric values are not considered here reducing the ration using Ch-OH, the latter scores better than NaOH in all other metrics (Table 8). These reductions are mainly caused either because of the absence of byproducts (*i.e.* E-factor), or because of the lower input mass requirements per kilogram of final choline chloride (namely mass intensity -MI-, process mass intensity -PMI-, process mass efficiency -PME-, mass productivity -MP-). Additionally, the higher requirements of raw materials also include water, which increases the demands of wastewater intensity (WWI) when using NaOH. In terms of the highest relative differences, E-factor and WWI show the largest increases, the first quadruplicated and the second by 50%. Overall, the use of Ch-OH outperforms the use of NaOH by 75% average.

In summary, while both NaOH- and Ch-OH-mediated syntheses of choline chloride follow similar chemical pathways, they differ significantly from a sustainability perspective. The Ch-OH route offers nearly double the productivity compared to the NaOH route, resulting in a reduced demand for reactants. This increased efficiency helps offset the higher environmental impacts associated with Ch-OH, which are greater than those of NaOH.

The DES in this work is compared with five similar Ch-Cl-based DESs on a mass basis. To synthesize similar DES, the urea, ethylene glycol (EG), glycerol (Gly), citric acid (CA), or glucose (Glu) are employed.<sup>42</sup> As shown in Table 9, the GWP of DES synthesis process in this work is lower than that of Ch-Cl:Gly and Ch-Cl:CA, but higher than that of Ch-Cl:Urea, Ch-Cl:EG, and Ch-Cl:Glu. EPw, HTP and ET of DES in this work is the smallest among all the DESs showed in Table 9. Conversion units were applied according to Owsianiak *et al.*<sup>43</sup>

**3.3.4. Environmental risk assessment (ERA).** As aforementioned, ecotoxicity and human toxicity categories were selected from the LCA as they are directly relevant for ERA. Nonetheless, ERA requires normalization and characterization of values (*e.g.*, kg 1,4-DCB-eq) into concentration units to allow for comparison, which is easily achieved during process design where all parameters are available. Continuous processing in general, and flow chemistry in particular help mitigate these risks due to the low volume processed at a given moment. The primary metric for ERA is the risk characterization ratio (RCR), calculated as the predicted environmental concentration (PEC) based on the process design, divided by the predicted no-effect concentration (PNEC). PNEC can be estimated taking LC<sub>50</sub> values as reference, namely the concentration lethal to 50% of organisms.<sup>44</sup> Whilst PEC refers to the concentration of the chemical in a specific environmental compartment (*e.g.*, air, water, soil) based on LCA inventory data, PNEC represents the concentration, typically derived from toxicological data, below



Table 7 Circularity metrics calculation to produce 1 kg choline chloride either using NaOH or Ch-OH as base

		NaOH	Ch-OH	Units
$M$	Mass of inputs	3.21	2.26	g
$F_R$	Fraction of mass of a product's feedstock from recycled sources	0.44	0.42	—
$V$	Virgin material, not coming from reuse or recycling	1.79	1.30	g
$C_U$	Fraction of mass of a product going into component reuse	0.35	0.34	—
$E_C$	Efficiency of the extracting process	0.80	0.80	—
$E_F$	Efficiency of the recycling process used to produce recycled feedstock	0.45	0.75	—
$W$	Mass of unrecoverable waste associated with a product	1.62	0.40	g
$W_0$	Mass of materials no longer recoverable	0.77	0.24	g
$W_F$	Mass of waste generated while recycling	1.70	0.32	g
LFI	Linear flow index (material flowing in a linear fashion)	0.47	0.36	—
$F(X)$	Utility factor built as a function of the utility $X$ of a product	0.9	0.9	—
<b>MCI</b>	<b>Material circularity indicator</b>	<b>0.58</b>	<b>0.67</b>	—

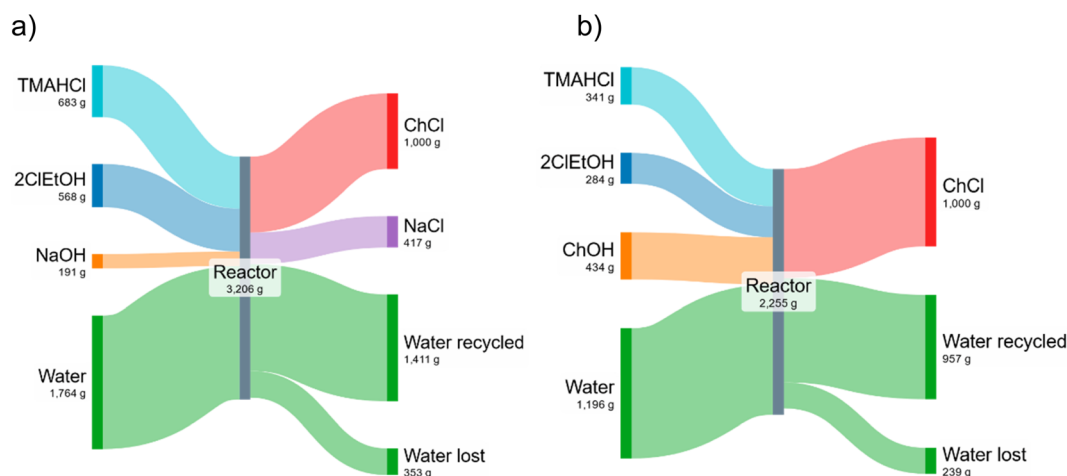


Fig. 10 Sankey diagrams of the mass flows distribution when operating in continuous flow, normalized for a production of 1 kg Ch-Cl with NaOH (a) or Ch-OH (b).

Table 8 Green chemistry metrics calculation for choline chloride production either using NaOH or Ch-OH as base

Metric	Concept	Abbrev.	NaOH	Ch-OH	Unit	Ideal
Atom economy	$\frac{MW(\text{product}) \times 100}{\sum MW(\text{reactants})}$	AE	78	54	%	100
Environmental impact factor	$\frac{\sum m(\text{waste generated})}{m(\text{product})}$	E-factor	0.4	0.1	kg kg <sup>-1</sup>	0
Mass intensity	$\frac{\sum m(\text{reactants})}{m(\text{product})}$	MI	1.4	1.1	kg kg <sup>-1</sup>	1
Process mass intensity	$\frac{\sum m(\text{reactants and water})}{m(\text{product})}$	PMI	3.2	2.3	kg kg <sup>-1</sup>	1
Process mass efficiency	$\frac{m(\text{product}) \times 100}{\sum m(\text{reactants and water})}$	PME	31	44	%	100
Mass productivity	$\frac{m(\text{product}) \times 100}{\sum m(\text{reactants})}$	MP	69	94	%	100
Wastewater intensity	$\frac{\sum m(\text{water})}{m(\text{product})}$	WWI	1.8	1.2	kg kg <sup>-1</sup>	0

which adverse effects on the ecosystem are not expected. Accordingly, RCR values below 1 assume the risk is considered as acceptable, while values higher or equal to 1 denote risks may be significant, and mitigation measures may be necessary.

For this study, 4 species were considered in the ERA assessment for both evaluated alternatives. LC<sub>50</sub> values were obtained from the safety data sheets provided by the chemical suppliers, while PEC calculations were derived from the process



**Table 9** DES synthesis process comparison (GWP = global warming potential (kg CO<sub>2</sub> eq.); EPw = eutrophication, freshwater (kg P eq.); HTP = human toxicity potential (CTUh); ET = ecotoxicity, freshwater (CTUe)). Based on ref. 42 and category units corrected based on ref. 43

	Ch-Cl:Urea	Ch-Cl:EG	Ch-Cl:Gly	Ch-Cl:CA	Ch-Cl:Glu	This work
GWP (kg CO <sub>2</sub> eq.)	$1.82 \times 10^0$	$2.00 \times 10^0$	$2.55 \times 10^0$	$4.3 \times 10^0$	$1.61 \times 10^0$	$2.18 \times 10^0$
EPw (kg P eq.)	$4.71 \times 10^{-4}$	$4.39 \times 10^{-4}$	$4.90 \times 10^{-4}$	$1.29 \times 10^{-3}$	$4.26 \times 10^{-4}$	$4.31 \times 10^{-5}$
HTP (kg 1,4-DCB eq.)	$5.17 \times 10^{-1}$	$4.69 \times 10^{-1}$	$4.69 \times 10^{-1}$	1.51E + 00	$4.44 \times 10^{-1}$	—
(CTUh)	$1.11 \times 10^{-7}$	$1.11 \times 10^{-7}$	$1.11 \times 10^{-7}$	$1.11 \times 10^{-7}$	$1.11 \times 10^{-7}$	$1.43 \times 10^{-8}$
ET (kg 1,4-DCB eq.)	$4.07 \times 10^{-2}$	$3.83 \times 10^{-2}$	$4.77 \times 10^{-2}$	$1.29 \times 10^{-1}$	$5.04 \times 10^{-2}$	—
(CTUe)	$3.99 \times 10^1$	$3.75 \times 10^1$	$4.68 \times 10^1$	$1.26 \times 10^2$	$4.94 \times 10^1$	$2.21 \times 10^1$

design herewith presented. As shown in Table 10, neither the starting material nor the base used for each alternative presents a significant environmental concern, since both RCR values scored much below 1 in all cases. However, 2ClEtOH exhibits high RCR values, indicating potential environmental risk. Although this compound is consumed during the reaction process, eliminating any risk associated with the final product, it may still pose a risk due to its use as a raw material. Further research should focus on identifying alternatives to the use of 2ClEtOH as a raw material.

These results contrast with the LCA outcomes shown in Fig. 11, which highlights the different nature of LCA and ERA assessments. In LCA, the largest contribution to environmental impacts from 2ClEtOH corresponds to ecotoxicity (32%) in the NaOH scenario and to human toxicity (non-cancer) in the Ch-OH scenario (30%). In other cases, TMAHCl exhibits the highest impacts. This difference is caused because, whilst LCA accumulates emissions and resource use across all life cycle stages to estimate potential impacts, it lacks the specificity to assess individual exposure pathways or local environmental conditions. Differently, ERA focuses on how a particular chemical or pollutant interacts with its immediate environment. In this context, both methods are complementary: LCA aids in identifying sources comprehensively, while ERA provides detailed risk insights for specific scenarios.

The ERA results contextualize Table 5 LCA findings, particularly regarding 2ClEtOH handling. While this raw material presents moderate ecotoxicity risks, the flow process's closed-system design effectively contains exposure potentials.

### 3.4. Technoeconomic assessment (TEA)

**3.4.1. Operation costs (OPEX).** Ch-Cl is produced industrially by reacting TMA, ethylene oxide (EO) and HCl in aqueous

phase. The synthesis is highly exothermic and is typically run in stirred, pressure-rated reactors with heat removal and tail-gas absorption of unreacted EO and TMA.<sup>45</sup> The base-case analysis (conventional or current process) considered a 50 kt a<sup>-1</sup> Ch-Cl plant operating 330 days per year in Europe, using the conventional EO-TMA-HCl route. Applying stoichiometric consumption corrected for a 96% overall yield,<sup>46</sup> mass-specific feed requirements were 0.329 t EO, 0.442 t TMA, and 0.272 t HCl per tonne of saleable Ch-Cl, in agreement with stoichiometric balances reported for similar plants. When combined with literature-consistent adjusted bulk feedstock prices, producers can offer 1000 USD per t EO, 1400 USD per t TMA, 120 USD per t HCl, amounting the raw-material cost 980.13 USD per t, equivalent to around 870 EUR per t. Utilities such as electricity for pumping, agitation, control, spray dryer fans (150 kWh per t), and steam/fuel for heating, evaporation and drying (833 kWh per t) accounted 12 USD per t and 18 USD per t respectively, while minor consumables contributed a further 40 USD per t, yielding a total variable cost of approximately 1050.13 USD per t.<sup>47</sup> Under a selling price of about 1200 USD per t (feed-grade, 75% solution equivalent), the revenue scores around 12.5%, leaving limited room to absorb fixed costs and capital charges. This result is consistent with commercial cost reports that identify raw materials as the dominant cost driver in Ch-Cl manufacture, with feedstocks representing more than 70% of the ex-works production cost. It also reflects the broader European chemical-industry context, where high energy and feedstock prices have reduced margins.<sup>48</sup>

**3.4.2. Capital investment (CAPEX).** For a 50 kt a<sup>-1</sup> reference plant, a mid-range specific investment of 2000 USD per tonne of annual capacity (1770 EUR per t a) taken from generic chemical-plant benchmarks yields a total installed CAPEX of 88.5 million EUR, which lies within the lower range of European specialty-

**Table 10** RCR calculation for each species involved in the reaction according to both studied scenarios (risk characterization ratio = RCR, predicted environmental concentration = PEC, predicted no-effect concentration = PNEC)

Compound	PNEC					PEC		RCR	
	CL <sub>50</sub>	Oral	Inhalation	Dermal	Animal test	NaOH	CH-OH	NaOH	CH-OH
TMAHCl	mg kg <sup>-1</sup>	3090	—	—	Rat	237	160	0.08	0.05
2ClEtOH	mg kg <sup>-1</sup>	71	0.11	67	Rat/rabbit	199	135	2.81	1.90
NaOH 50%	mg kg <sup>-1</sup>	2000	5	2000	Rat	99	—	0.05	—
CH-OH	mg kg <sup>-1</sup>	11000	—	21.4	Rat	—	203	—	0.02



chemical investments when compared with similar-scale plants reported in recent CAPEX analyses.<sup>49</sup> Assuming a project lifetime of 20 years and a 10% discount rate, the capital recovery factor of 0.117 results in an annualized capital charge of about 11.7 million USD a<sup>-1</sup> (10.4 million EUR a<sup>-1</sup>), equivalent to 234 USD per t (210 EUR per t) of product at full capacity.<sup>50</sup> Fixed operating costs were estimated using standard percentage-of-investment applied in industrial cost-estimation practice.<sup>51</sup> Maintenance was taken as 4% of CAPEX per year and combined labour, supervision, overhead, and insurance as 5% of CAPEX, giving a total fixed OPEX of 8 million a<sup>-1</sup> (7.1 million EUR a<sup>-1</sup>), or roughly 180 USD per t (140 EUR per t) at nameplate capacity.

Summing variable costs (1050 USD per t), fixed OPEX (180 USD per t), and annualized capital charges (234 USD per t) yields a levelized production cost of approximately 1464 USD per t (1297 EUR per t), exceeding the assumed market price of 1200 USD per t (1060 EUR per t) by about 200 USD per t. Under these conditions, the project would not be economically attractive without either higher realized product prices or significant reductions in CAPEX and/or feedstock costs. This outcome aligns with independent cost reports indicating that choline chloride production in Europe is highly sensitive to site-specific investment levels and feedstock procurement strategies.<sup>48</sup>

A second scenario explored the effect of a more optimistic specific investment of 1200 USD per (t a), representative of debottlenecking-type projects or low-cost locations within Europe. Converted to euros, this corresponds to 1060 EUR per (t a) and a total CAPEX of 53 million EUR, leading to an annualized capital charge of 6.2 million EUR a<sup>-1</sup> ( $\approx$  125 EUR/t) and fixed OPEX of about 4.8 million EUR a<sup>-1</sup> ( $\approx$  95 EUR/t). The resulting LPC in this low-CAPEX scenario drops to around 1130 EUR per t, slightly above the base selling price but compatible with profitability if market prices reach or exceed 1200–1300 EUR per t for certain grades or contract structures.<sup>52</sup>

**3.4.3. Comparison with the current study.** The TEA results for the conventional Ch-Cl production process were benchmarked with the two novel pathways highlighted in this study (NaOH and Ch-OH routes). Table 11 summarizes the operating expenditure (OPEX) costs per tonne of Ch-Cl across these scenarios, assuming comparable capital expenditures (CAPEX), electricity-based energy accounting in the novel routes, and a common spray-drying step for final purification.

In the conventional process, trimethylamine and ethylene oxide dominate costs (947.50 USD per t combined), reflecting their stoichiometric demands.<sup>48</sup> The NaOH route substitutes these with 2ClEtOH (544.63 USD per t), TMAHCl, and NaOH, yielding a slightly higher total (1114.34 USD per t; +6% vs. conventional) due to elevated 2ClEtOH pricing despite TMA reductions. The Ch-OH route, included for contextual linkage (though outside this paper scope), generates Ch-OH from TMA and ethylene oxide in water, followed by reaction with trimethylamine hydrochloride and 2ClEtOH at double productivity, subsequently halving key feedstock inputs (*e.g.*, TMA and EO to  $\sim$ 164 USD per t each; 2ClEtOH to 272.32 USD per t) and achieving the lowest OPEX at 579.76 USD per t (45% reduction, or 470.37 USD per t savings vs. conventional).

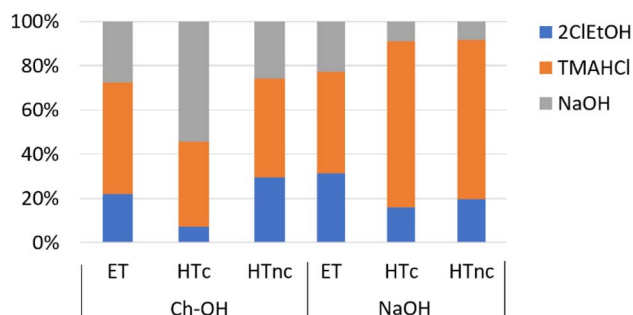


Fig. 11 LCA contributions exclusively concerning ecotoxicity (ET) and human toxicity (HT), including cancer (HTc) and non-cancer (HTnc).

Other variable costs were held constant across scenarios to isolate feedstock and utility effects. Electricity costs rise markedly in novel routes (101.60 USD per t), likely from direct linearly scaled laboratory experiments, but Ch-OH productivity gain mitigated this per-tonne burden; steam elimination further offset conventional utilities.

As shown in Fig. 12, at a bulk selling price of *ca.* 1200 USD per t, the Ch-OH route delivered the strongest gross margin (620.24 USD per t; 52% of revenue), followed by conventional (149.87 USD per t; 12.5%) and NaOH route (85.66 USD per t; 7%). These alternatives mitigate ethylene oxide hazards, since NaOH route directly avoids its use by employing 2ClEtOH, while Ch-OH route uses the half of ethylene oxide just in the previous stage (outside this paper scope) to yield Ch-OH intermediate before chloride incorporation. Feedstock shifts drive the economics, conventional reliance on volatile ethylene oxide/TMA gives way to 2ClEtOH dominance in NaOH/Ch-OH, with Ch-OH efficiency providing a clear edge. Sensitivity analysis denotes a high dependence on 2ClEtOH and TMA prices depending on the synthesis route. Despite not being the most economically advantageous route, the CH-OH exhibits the most balanced route when balancing costs, safety and environmental derived essentially from the absence of byproduct generation, increasing sustainability.

Table 11 OPEX calculations for the production of 1 tonne of choline chloride by three routes described in this paper: conventional, NaOH route and Ch-OH route

Item	Conventional (\$)	This work	
		NaOH	Ch-OH
Trimethylamine	618.33	—	308.97
Ethylene oxide	329.17	—	164.46
Hydrochloric acid	32.63	—	—
Trimethylamine hydrochloride	—	2.75	1.38
NaOH	—	116.39	—
2-Chloroethanol	—	544.63	272.32
Electricity	12.00	101.60	101.60
Steam and fuel	18.00	—	—
Other variable costs	40.00	40.00	40.00
<b>Total OPEX</b>	<b>1050.13</b>	<b>1114.34</b>	<b>579.76</b>



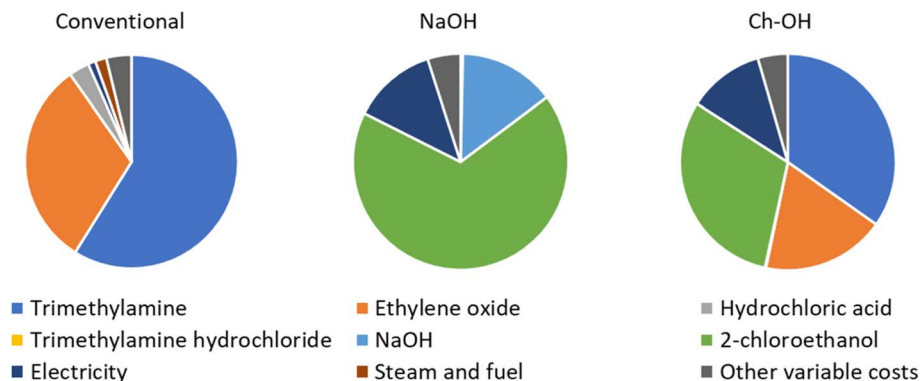


Fig. 12 Influence and cost contributions of each boundary in the OPEX calculation for each synthesis route.

## 4 Conclusions

This study proposes a significant process advance in the synthesis of choline chloride, which is a key constituent of natural deep eutectic solvents (NADES) and thereby advances the NADES synthesis as well. One green chemistry target in the pharmaceutical industry is to replace organic solvents that might cause environmental pollution with biodegradable and biocompatible alternatives. This study demonstrated process intensification *via* flow chemistry for the synthesis of choline chloride, when reducing residence times by a factor of 20 as compared with the corresponding batch processing at the same temperature. 99% yield and full conversion was achieved in 1 minute, and a purification process was developed with a final yield of 77% pure choline chloride. The production was performed using two alternatives regarding the base material: either with sodium hydroxide or choline hydroxide. The choline hydroxide-based processing achieved double productivity, of about half ton choline chloride per year with just one coil and produced no byproducts. A holistic sustainability assessment reported a 24% decrease on all environmental impacts in average when using choline hydroxide as compared with NaOH, normalized both to 1 kg production. Improved scores included 9 out of 11 impact categories in this study. The carbon footprint was reduced to 2.18 kg CO<sub>2</sub>-eq kg<sup>-1</sup> when using choline chloride. A key to sustainability was the double molar production per mol of initial trimethylamine hydrochloride when using choline hydroxide. Additionally, 51% energy reduction was achieved when using choline hydroxide. Circularity metrics when using choline hydroxide were similarly improved, achieving a material circularity indicator, MCI, of 0.67. This indicates that using Ch-OH improves material circularity by 10% compared to NaOH, primarily due to reduced waste generation and lower raw material input, demonstrating a more efficient and sustainable process within the circular economy framework. Green chemistry metrics were also derived, with an E-factor of 0.1, and the process mass index (PMI) of 2.26 kg kg<sup>-1</sup>, leading Ch-OH outperforming NaOH by an average of 75%. The environmental risk assessment only denoted concerns in the use of 2ClEtOH as raw material due to full consumption during the process, scoring RCR values above 1. Over the synthetic routes addressed, the CH-OH

exhibited the most balanced route when balancing costs, safety and environmental derived essentially from the absence of byproduct generation, increasing sustainability. It can be concluded that while the use of choline hydroxide increases environmental impacts derived from its production, this drawback is more than counterbalanced by the doubled productivity, reduced raw material demands, and absence of byproducts.

## Author contributions

Marc Escrivà-Gelonch: conceptualization, investigation, validation, methodology, project administration and writing – original draft. Volker Hessel: validation, co-supervision, edition, polishing and text revision. Nguyen Van Duc Long: investigation, edition, polishing and text revision. Ramon Canela-Garayoa: supervision, conceptualization, data curation and validation.

## Conflicts of interest

There are no conflicts to declare.

## Data availability

The software used for life cycle assessment are GaBi with Ecoinvent database. These softwares are available under license of the suppliers. Data for this article are available at the repository of University of Lleida <https://repositori.udl.cat/home>.

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