

Critical Assessment of the Sustainability of Deep Eutectic Solvents: A Case Study on Six Choline Chloride-Based Mixtures

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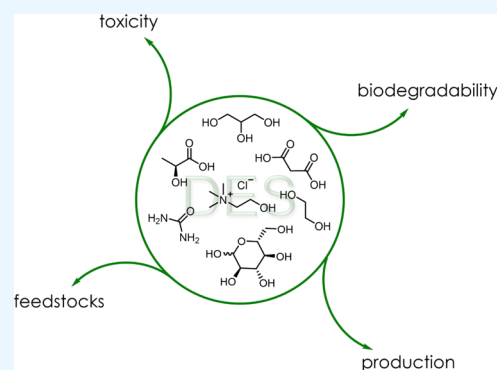
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ABSTRACT: An outline of the advantages, in terms of sustainability, of Deep Eutectic Solvents (DESs) is provided, by analyzing some of the most popular DESs, obtained by the combination of choline chloride, as a hydrogen bond acceptor, and six hydrogen bond donors. The analysis is articulated into four main issues related to sustainability, which are recurrently mentioned in the literature, but are often taken for granted without any further critical elaboration, as the prominent green features of DESs: their low toxicity, good biodegradability, renewable sourcing, and low cost. This contribution is intended to provide a more tangible, evidence-based evaluation of the actual green credentials of the considered DESs, to reinforce or question their supposed sustainability, also in mutual comparison with one another.



1. INTRODUCTION

One of the most relevant issues in green chemistry concerns the massive use of solvents, which are extensively employed in chemical processes at any level. Conventional organic solvents are mainly represented by volatile organic compounds (VOCs), which are generally regarded as non-sustainable, due to the hazards posed by their flammability and their toxicity toward human health and the environment, as well as to their non-renewable petrochemical production (with few exceptions).¹ In the search for alternatives to VOCs, Deep Eutectic Solvents (DESs) have emerged at the beginning of the present century and have rapidly garnered the interest of the scientific community.² Thanks to its peculiar and tunable properties, this class of solvents has found application in different fields, ranging from organic synthesis, including enzymatic catalysis, to drug dissolution and delivery, from biomass processing to gas capture, and from extraction processes to electrochemistry, including energy storage.³ A DES is a mixture of at least two components, one of which acts as Hydrogen Bond Acceptor (HBA) and one as Hydrogen Bond Donor (HBD). At a specific molar ratio of the components, the mixture shows a significant depression of the melting point (deep eutectic).⁴ Ever since the first reports, the potential of DESs as sustainable solvent systems has been pointed out.^{2a,5} Their components are usually small molecules, such as alcohols, short-chain carboxylic acids, amides, sugars, and abundant in nature, often as plant metabolites; the most common HBA, choline chloride (ChCl), is used as an additive for domestic animal feed.⁶ On this basis, there is a general

claim on the sustainability of DESs, which is usually expressed in terms of “low toxicity, high biodegradability, low cost, sourcing from renewable feedstock”. However, this general claim is rather vague and rarely supported by solid evidence, as it is often uncritically taken for granted by papers reporting new scientific developments and applications of DESs. Moreover, the supposed green credentials may vary significantly according to the nature of the components of the eutectic mixture. The present contribution aims at providing a comparative evaluation of the sustainable features of DESs, by choosing ChCl as HBA and six commonly employed HBDs, reported in Figure 1: glycerol (Gly, HBD₁), ethylene glycol (EG, HBD₂), urea (U, HBD₃), glucose (Glu, HBD₄), malonic acid (MA, HBD₅), and lactic acid (LA, HBD₆).

It is worth remembering that sustainability is a concept encompassing several aspects, as stated by the sustainable development goals, outlined by the United Nations in the 2030 Agenda for Sustainable Development.⁷ Therefore, this work is intended to critically discuss and address point by point the aforementioned claims, which have all contributed to define DESs as sustainable solvents, by discussing each of the “green” features (toxicity, biodegradability, renewable feedstocks,

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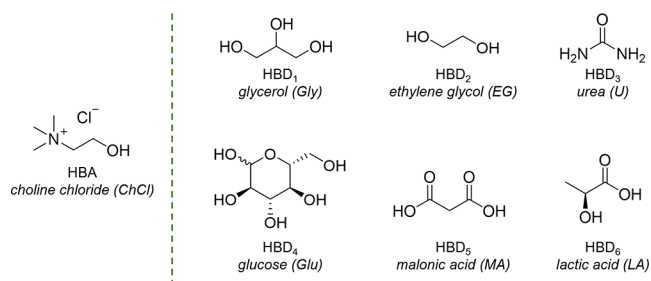


Figure 1. Hydrogen bond acceptor (HBA) and hydrogen bond donor (HBD) components of the DESs considered in this review.

production) in separate sections. Moreover, the comparison among different DESs is meant to point out in which respect they are comparable and in which they differ from one another from the point of view of sustainability. It should be noted that there is an ongoing debate to define in a more rigorous way under which conditions an eutectic mixture can be rightfully called a deep eutectic solvent; this discussion also involves, but is not limited to, how “deep” should the eutectic be, particularly when one of the components is already liquid at room temperature.⁸ On this basis, not all the molar ratios of ChCl and HBD_{1–6} reported in the literature could be correctly defined as DESs. However, from an application perspective it seems reasonable to include in the present discussion studies performed on ChCl/HBD_{1–6} mixtures at several molar ratios and not only in the proper “eutectic” composition, considering that lots of physical properties (the simplest being the existence in the liquid state) are shared among many compositions. Yet, in so doing, it would be more correct to term such systems as “DES-like”.

2. TOXICITY

The effects that the solvents used in industrial and technological applications induce on living organisms represent a concern for the environment, mainly through contamination of waters and soils, and ultimately for human health. Among the features that have raised interest around DESs as promising

alternatives to classical solvents is their supposed low toxicity, which would represent an improvement not only over VOCs but also over common Ionic Liquids (ILs), such as imidazolium- or pyridinium-based ones.⁹ The debate on the toxicity of DESs started from the observation that their components are in most cases abundant in nature as environmentally friendly plant metabolites. As summarized in Table 1, safety data sheets of these compounds do not highlight particular concerns for human handling, apart from the well-known acute oral toxicity reported for EG. The ecotoxicity, usually assessed through the effects produced on fish or other aquatic organisms, is negligible as well (Table 1).

However, it is now well established that synergistic effects of the components when combined in a DES could alter the properties of the mixture, because of the emerging interactions in the supramolecular structure of the eutectic mixture, characterized by a network of hydrogen bonds.¹⁰ The toxicity of a DES could then be different from that of its components: it thus becomes necessary to evaluate the safety profile of each system. To date, several studies have tried to shed light on the actual toxicity of various DESs, by investigating the effects on human and animal cell lines, microorganisms, including bacterial, yeast and fungi strains, and marine animal models. However, results from different works do not always point toward the same direction, and a lack of systematicity, also concerning the methods used to assess DESs toxicity, has recently been highlighted.¹¹ In the present paragraph, the available data on ChCl/HBD_{1–6} are compared to define whether one or more among them could be able to meet the definition of an “environmentally friendly solvent”. Since microbial toxicity has recently been the object of a comprehensive review,^{11b} hereafter the discussion will focus on toxicity toward animal models. In addition to that, two studies on the toxicity toward plant species (phytotoxicity) are included. Table 2 summarizes the available data concerning the effects induced by ChCl/HBD_{1–6} DESs on animals. In 2013, 10 years after DESs had made their way into the scientific debate,^{2a} the first investigation to evaluate their actual ecotoxicological profile was conducted on the brine shrimp

Table 1. Available Information, from Safety Data Sheet, on the Toxicity of ChCl and HBD_{1–6}^a

Component	CLP classification ^b	Acute toxicity to rat (oral LD ₅₀ ^c)	Toxicity to fish (LC ₅₀ ^d)
ChCl (HBA)	Not a hazardous substance	LD ₅₀ = 3.40 g/kg ^e	No data available
Gly (HBD ₁)	Not a hazardous substance	LD ₅₀ = 27.2 g/kg	LC ₅₀ = 54000 mg/L Rainbow trout (<i>Oncorhynchus mykiss</i>) Static test, 96 h
EG (HBD ₂)	Acute toxicity, oral (category 4) Specific target organ toxicity, repeated exposure, oral (category 2), kidney	No data available	LC ₅₀ = 72860 mg/L Fathead minnow (<i>Pimephales promelas</i>) Static test, 96 h
U (HBD ₃)	Not a hazardous substance	LD ₅₀ = 8.47 g/kg	No data available
Glu (HBD ₄)	Not a hazardous substance	LD ₅₀ = 25.8 g/kg	No data available
MA (HBD ₅)	Serious eye damage (category 1)	LD ₅₀ = 3.25 g/kg	LC ₅₀ = 95.4 mg/L Japanese rice fish (<i>Oryzias latipes</i>) Flow-through test, 96 h
LA (HBD ₆)	Skin irritation (category 2) Serious eye damage (category 1)	LD ₅₀ = 3.54 g/kg	LC ₅₀ = 130 mg/L, Rainbow trout (<i>Oncorhynchus mykiss</i>) Static test, 96 h

^aSafety data sheet available at Sigma-Aldrich Web site. ^bAccording to EC Regulation No. 1272/2008 (CLP/GHS). The definition of the categories for each class of hazard are included in the text of the Regulation. ^cAmount of substance that kills 50% of test animals in a single dose. ^dConcentration at which 50% mortality occurs. ^eOral LD₅₀ to mice: 3.90 g/kg.

Table 2. Toxicity of ChCl/HBD₁₋₅ DESs Towards Animal Models^a

Animal model	DES		Results	Ref.	
	Components	Ratio			
Brine shrimp (<i>Artemia salina</i>)	ChCl/Gly	1/3	<ul style="list-style-type: none"> All DESs were toxic Higher toxicity for DESs than for components alone or their mixture 	12a	
	ChCl/EG	1/3			
	ChCl/U	1/3			
Hydra (<i>Hydra sinensis</i>)	ChCl/Gly	Various ^b	<ul style="list-style-type: none"> All DESs were toxic Lower toxicity for DESs than for components alone (particularly ChCl) or their mixture 	13	
	ChCl/EG	Various ^b			
	ChCl/U	Various ^b			
Crustacean (<i>Daphnia magna</i>)			EC ₅₀ (mg/L)	14a	
	ChCl/Gly	1/2	2530		
	ChCl/EG	1/2	1870		
Fish (<i>Cyprinus carpio</i>)				15	
	ChCl/U	1/2	1100		
	ChCl/Gly	1/2, 1/3	>100		<ul style="list-style-type: none"> All DESs were “practically harmless”, as well as their components alone or their mixture
	ChCl/EG	1/2, 1/3	>100		
	ChCl/U	1/2	>100		
					LC ₅₀ (mg/L)
ChCl/Glu	2/1	>100	<ul style="list-style-type: none"> Among DES components, slight toxicity for MA solution (LC₅₀ = 50 ± 15 mg/L) and ChCl + MA solution (LC₅₀ = 55 ± 13 mg/L) 		
ChCl/MA	1/1	>100			
Mice			LD ₅₀ (g/kg)	17	
	ChCl/Gly	1/3	6.39 ± 0.53		
		1/2	7.73 ^c		
	ChCl/EG	1/3	5.33 ± 0.49		
	ChCl/U	1/3	toxic		
	1/2	5.46 ± 0.36			

^aAll other DESs studied in the considered papers are not reported. ^b1/1, 1/2, 2/1 ratios were tested, without significant differences from one another. ^c95% confidence interval: 7.13–8.39 g/kg.^{17c}

Artemia salina, an assay which evaluates the survival rate of the shrimp's nauplii as a function of time after immersion in a solution of the potentially toxic agent.¹² The results showed that solutions of the three tested DESs, ChCl/HBD₁₋₃ in a 1/3 molar ratio, were harmful toward this organism, and their toxicity was significantly higher than that of solutions of both their components alone and of the simple mixture of their components (without the prior formation of the eutectic). It should be pointed out that the brine shrimp assay involves the monitoring of the survival rate of the shrimp's nauplii after several hours or days,^{12b-d} while in this case all organisms were found dead after minutes or tents of minutes. Furthermore, the authors did not include a control group in the experiment, to exclude other possible reasons for the toxicity, and did not report the concentration of the DESs in the solutions used for the assay: thus, no reliable LC₅₀ (lethal concentration, at which 50% mortality occurs) values could be provided. These data should then be considered as a preliminary assessment of the toxicity and a starting point for further investigations, suggesting that the synergistic effect could lead to a toxicity enhancement of the system, probably due to the involvement of ChCl and HBDs in the eutectic mixture. This point is of paramount importance to design suitable procedures for DES-containing waste treatment, for example, through dilution in aqueous medium and subsequent disruption of the supra-molecular structure. Following efforts were focused on the toxicity toward other aquatic species, such as *Hydra sinensis*, a freshwater invertebrate.¹³ Again, DESs (or DES-like mixtures) composed of ChCl and HBD₁₋₃ (in 1/1, 1/2, and 2/1 molar ratios) were tested (Table 2). In all cases, the exposition to a 10 mM concentration of the DESs caused significant shortenings in the survival times of the hydras, compared to

the control group; in addition, before death, the morphology of the organisms underwent the changes typical of exposure to a toxic chemical. Interestingly, while the HBD₁₋₃ solutions displayed limited toxicity, ChCl proved to be much more lethal than the DESs; the components ChCl and HBD₁₋₃, mixed together in solution but without prior formation of the eutectic, were also as toxic as the choline salt alone. In this case, then, a synergistic effect of the DES appears to be able to mitigate the toxicity of the most harmful component by incorporating it in the eutectic structure, in an opposite way to that observed in the *A. salina* assay. However, it should be observed that the DES concentration in the solution into which the organisms were immersed was quite high (10 mM, i.e., in the range 2000–4000 mg/L depending on the considered DES): studies within a range of concentrations would be necessary to determine LC₅₀ values. Among aquatic invertebrates, the toxicity of three DESs, ChCl/HBD₁₋₃ in a 1/2 molar ratio, was studied also on the planktonic crustacean *Daphnia magna*. The test, conducted according to OECD Guideline No. 202, evaluated the immobilization of the organisms after 24 h of exposition to different concentrations of the considered DESs.¹⁴ According to the results, expressed as EC₅₀ (half maximal effective concentration), the three eutectic mixtures could be classified as “relatively harmless”, with EC₅₀ values higher than 1000 mg/L (Table 2). Noteworthy, significant differences were observed with different HBDs, as ChCl/Gly had an EC₅₀ value more than twice greater than ChCl/U.^{14a} The acute toxicity (expressed as LC₅₀) of DESs composed of ChCl and HBD₁₋₅ (in various molar ratios, see Table 2) on a fish model, the Eurasian carp (*Cyprinus carpio*), was investigated in two different papers.¹⁵ In sharp contrast with the experiments on *A. salina* and *H.*

Table 3. Phytotoxicity of ChCl/HBD_{1–4} DESs^a

Plant	DES		Results	Ref.
	Components	Ratio		
Garlic (<i>Allium sativum</i>)	ChCl/Gly	1/1	<ul style="list-style-type: none"> • Root growth inhibition by DESs as well as their components • High toxicity of ChCl, mitigated in ChCl/U, but not in ChCl/EG • ChCl/Gly significantly less toxic than <i>both</i> its components 	13b
	ChCl/EG	1/1		
	ChCl/U	1/1		
Wheat (<i>Triticum aestivum</i>)	ChCl/Gly	1/2	<ul style="list-style-type: none"> • Practically harmless toward seed germination • Relatively higher toxicity for shoot and root growth inhibition 	19
	ChCl/Glu	2/1		

^aAll other DESs studied in the considered papers are not reported.

sinensis, and in accordance with that on *D. magna*, all tested DESs were practically harmless: the LC₅₀ values were higher than 100 mg/L in all cases. Indeed, the tests were conducted according to the OECD Guideline No. 203 for fish acute toxicity, which poses 100 mg/L as a threshold above which it is not necessary to determine the exact LC₅₀ figure.¹⁶ Nevertheless, the latter was calculated for three systems only, namely ChCl/Gly, ChCl/EG, and ChCl/U in 1/2 molar ratio, resulting in values in the 6000–10000 mg/L range.^{15a} Similarly, the single components, as well as their mixtures without prior eutectic formation, showed no significant effects on the fishes, in line with low ecotoxicities reported in the safety data sheets (Table 1). The only exception was MA, which revealed to be slightly toxic (again, in line with what reported in Table 1) when not incorporated into a DES, highlighting a synergistic mitigation by the eutectic mixture.^{15b} Finally, DESs composed by ChCl and HBD_{1–4} were tested for the toxicity toward mice.¹⁷ The LD₅₀ (lethal dose, the amount of a solid or liquid material that kills 50% of test animals in a single dose) values after oral administration (Table 2) showed that the considered DESs are relatively toxic, with an approximative two-/four-fold decrease compared with the components alone. The authors observed a correlation between the toxicity and the ChCl/HBD molar ratio, as in the case of ChCl/U 1/3 the lethality was so fast that it did not allow the determination of the LD₅₀, while the 1/2 ratio was revealed to be less toxic.^{17a} It should as well be considered that, for ChCl/U, the 1/2 ratio is the one that identifies the “proper” DES composition, and its reduced toxicity could then arise from inherent synergistic effect in the deep eutectic mixture. The metabolomics analysis of the treated mice was also evaluated, revealing acute liver and kidney injury, associated with elevated oxidative stress.^{17a,b} Moreover, stress response to ammonia exposure was detected after the oral administration of ChCl/U 1/2, at a dose of 1.5 g/kg; the authors traced this back to ammonia impurities present in the urea used to produce the DES, hypothesizing that the absorption and toxicity of this chemical could be enhanced by the presence of the DES itself.^{17b} On this basis, it is possible that ammonia stress is involved in the higher toxicity of ChCl/U 1/3, compared to ChCl/U 1/2 (Table 2). Apart from ChCl/HBD_{1–3}, also the toxicity of the sugar-based ChCl/Glu 2/1 was tested.¹⁸ However, in the paper, there is a discordance between the materials and methods and the results sections, which poses doubts on whether the authors evaluated the toxicity upon oral or parenteral administration of the mixtures (the latter is more likely, according to the authors’ discussion). For this reason, the results are not included in Table 2. The investigation of the compatibility of DESs with parenteral administration is more focused on the possible use of the eutectics as drug delivery systems, rather than on their ecotoxicity.^{3d,e}

Alongside studies on animals, the phytotoxicity of DESs was evaluated with testing garlic (*Allium sativum*)^{13b} and wheat (*Triticum aestivum*)¹⁹ as specimen; the results are summarized in Table 3. In the case of garlic, the effect of ChCl/HBD_{1–3} 1/1 DESs on germination from garlic cloves was evaluated by measuring the root growth inhibition after soaking in the DES solution. The results showed that all DESs were harmful toward the root growth, as well as their components, among which U was the less toxic, while ChCl and Gly had the worst effect: it is then particularly noteworthy that the ChCl/Gly DES displayed a synergistic effect such that its toxicity was significantly lower than both its two components.^{13b} Regarding the *T. aestivum* experiment, three parameters were monitored after treatment with different concentrations of DESs: the seed germination, and the root and shoot growth of the seedling after germination. It was found that both ChCl/Gly 1/2 and ChCl/Glu 2/1 were practically harmless toward seed germination (EC₅₀ > 20000 mg/L), while some root and shoot growth inhibition was observed (EC₅₀ ≈ 800–3700 mg/L), with roots being more sensitive than shoots. This was explained by the direct contact of roots with the DES solutions. The study did not evaluate the toxicity of single DES precursors.¹⁹ It should be noted that another work by the same group revealed lower values of EC₅₀ for imidazolium-based ILs, using barley (*Hordeum vulgare*) as a plant model, confirming the higher phytotoxicity of the ILs compared to the above-mentioned DESs.²⁰

The analysis of available information on the toxicity of DESs on animal and plant species reveals different possible scenarios, in which the hazard of the eutectic mixtures may be higher, lower, or equal compared to their components alone. It is now diffusely recognized that the initial assumption of DESs as generically “environmentally friendly”, based on the nature of their constituents, is somehow *naïve*. As a matter of fact, the studies reported in this chapter indicate that even these apparently harmless compounds may represent a concern for the environment, and the cases of ChCl toxicity toward hydra (Table 2) and garlic (Table 3) are illustrative in this regard. The matter could be particularly relevant in case DESs were used as solvents in large-scale applications, because of their amount in waste effluents, which could result in high concentrations in the environment. Furthermore, as suggested by some of the results presented in this chapter and by studies on microbial toxicity, the peculiar physicochemical properties of DESs, such as their viscosity, may have a role in altering their intrinsic chemical toxicity and their ability to constitute a hazard for the environment. Indeed, a rigorous evaluation of the safety of DESs should involve an effort not only in trying to apply standard procedures to produce comparable data, as remarkably done for example in the carp toxicity studies, but also in establishing new general guidelines to take into account the nature and the characteristics of these mixtures.^{11a,b} In

Table 4. Biodegradability of ChCl/HBD₁₋₅ DESs

	Ratio	Conc. (mg/L)	Results		Ref.
			% ThOD	day	
ChCl/Gly	1/2	3	83	14	23b
			96	28	
	1/2	5	91	28 ^a	15a
			84	7	
	1/2	100	96	28	19
			60 ^b	4	
	1/2	100	70–80 ^b	28	
ChCl/U	1/1	3	85	14	23a
			95	28	
	1/1	4	40–50	28 ^a	13b
ChCl/EG	1/2	3	58	14	23b
			82	28	
	1/2	5	75–80	28 ^a	15a
			60 ^b	8	
	1/2	100	70–80 ^b	28	
	1/1	4	20–30	28 ^a	13b

	Ratio	Conc. (mg/L)	Results		Ref.
			% ThOD	day	
ChCl/U	1/2	3	81	14	23b
			97	28	
	1/2	5	85	28 ^a	15a
			60 ^b	7	
	1/2	100	60–70 ^b	28	
	1/1	4	75–80	28 ^a	13b
60–70			7	19	
2/1	100	≈80	28		
ChCl/Glu	2/5	3	79	14	23a
			91	28	
ChCl/MA	1/1	3	50	14	23b
			76	28	

**Closed bottle test**

Test chemical (at a certain conc.) incubated with the microorganism-containing water.

% ThOD (= BOD/ThOD) determined at different time intervals (day).

^aNot explicitly stated in the paper. ^bObtained through manometric respirometry (OECD 301 F) instead of a closed bottle test (OECD 301 D).²²

conclusion, it seems premature to make a pronouncement on the actual toxicity of DESs. However, it is worth mentioning that the available data on ecotoxicity toward aquatic organisms are encouraging, with LC₅₀ values in the order of 10²–10³ mg/L (Table 2). Among those considered in this review, the studies in which some differences were observed highlighted that MA could be a relatively more harmful HBD (the only one to display some toxicity in the *C. carpio* studies), as highlighted also in Table 1, while U appeared much safer than others in the *A. sativum* works (Table 3). One point that certainly identifies DESs as safe and environmentally friendly is their negligible vapor pressure, which excludes the possibility of atmospheric contamination and hazards deriving from inhalation.²¹

3. BIODEGRADABILITY

The discussion on the biodegradability of DESs takes its cues from the same assumptions that have been enunciated regarding their toxicity: since their components are plant metabolites, present in variable amounts in the environment and in biological systems, they should get easily degraded by naturally occurring microorganisms. The assessment of the persistence of a substance in the environment is once again particularly important to design suitable protocols for waste treatment, especially in the case of solvents, whose disposal may involve large amounts of substance. Under this point of view, it would be of course desirable to replace non-biodegradable conventional solvents with “endogenous” ones. The DES components considered in this review are classified as “readily biodegradable” by their safety data sheet, except for malonic acid and urea, for which no data are available (anyway, they are classified as not persistent in the environment). As for toxicity, however, also the biodegradability of DESs cannot be taken for granted and should be evaluated on a case-by-case basis. Up to now, the topic has been investigated in some

studies, all of which were conducted according to OECD Guideline No. 301 D (namely, the “closed bottle test”), that allows classifying a chemical as “readily biodegradable” or not in an aerobic aqueous medium.²² The experiment consists of adding the test chemical, previously dissolved into a saline solution, to a bottle containing an inoculum, i.e., a water sample collected from a secondary effluent of a wastewater treatment plant or from surface water (e.g., of a lake), diluted with deionized or distilled water. The bottle is closed and stored in the dark, and the amount of dissolved O₂ is measured at different time intervals to determine the biochemical oxygen demand (BOD, the amount of O₂ consumed by aerobic organisms to metabolize organic matter) by comparison with a blank solution, not containing the test chemical. The BOD value is then used to calculate the percentage of the theoretical oxygen demand (ThOD), which is based on the mass and molecular formula of the chemical employed. If this percentage reaches 60% in a 14-days window, starting from the day in which it has reached 10%, and not exceeding the 28th day from the beginning of the experiment, the test chemical can be considered as “readily biodegradable”. To validate the results, the experiment is also performed on a reference compound, which is known to meet the criteria for ready biodegradability: if such compound reaches the pass level (60% ThOD) within 14 days, the test is considered valid.²² The results from the different papers in which the biodegradability of ChCl/HBD₁₋₅ DESs has been investigated are summarized in Table 4. First of all, it should be noted that the criteria for ready biodegradability are met in almost all cases, with high levels of % ThOD not only at 28 days from the beginning of the experiment but also after 14 or even 7 days. In one work only, ChCl/Gly and ChCl/EG DESs, both in a 1/1 molar ratio, failed to reach the pass level.^{13b} The authors attributed this significant discrepancy to different experimental conditions and different source and concentration of the inoculum, even if

their experiment was successfully validated with sodium benzoate as a reference compound, obtaining results comparable to other studies.²³ The effects of microbial populations coming from different sites have also been pointed out by a study on pyridinium and imidazolium-based ILs.²⁴

Beyond the definition of “readily biodegradable”, that is common to all the considered DESs in Table 4, some differences can be highlighted, according to the nature of the HBD component. ChCl/Gly and ChCl/U show the highest biodegradability values: under the same experimental conditions, ChCl/Gly 1/2 and ChCl/U 1/2 (at a 3 mg/L concentration) showed % ThOD values of 96% and 97% respectively, while ChCl/EG 1/2 and ChCl/MA 1/1 were one step below, with 82% and 76% ThOD respectively, after 28 days. Remarkably, the difference was even greater in the first 14 days, with 83% and 81% for Gly- and U-based DESs, while ChCl/EG only reached 58%, similarly to the 50% ThOD for ChCl/MA (Table 4).^{23b} A similar trend was observed with the same DESs at a 5 mg/L concentration (91% for ChCl/Gly, 85% for ChCl/U, 75–80% for ChCl/EG).^{15a} These slight differences have been interpreted according to the Boethling’s rules of thumb for designing biodegradable small molecules,²⁵ since a higher number of hydroxyl groups per mole (Gly vs EG) or the presence of carboxylic derivatives, such as acids, esters, or amides (as in the case of U) should improve the biodegradability profile. For MA-based DES, acidification of the aqueous medium was invoked to account for the less efficient biodegradation.^{15a,23b} High values of % ThOD were obtained also with Glu as HBD: under the same experimental conditions, ChCl/Glu 2/5 and ChCl/Gly 1/1 (at a 3 mg/L concentration) reached 79% and 85% ThOD respectively after just 14 days, and more than 90% after 28 days (Table 4).^{23a} It appears then that the issue on the biodegradability of DESs is less controversial than the one on toxicity: the available literature data point toward the definition of “readily biodegradable” for the considered ChCl/HBD_{1–5} DESs, in particular for Gly, U, and Glu as HBDs, with EG and MA just immediately following. To the best of our knowledge, no biodegradability studies were performed on LA-based DESs. Interestingly, this green feature is shared with a series of ILs composed of choline as the cation and 19 amino acids as the anion, in contrast with the often low biodegradability of more classical pyridinium- or imidazolium-based ILs.²⁶ This suggests that the use of naturally occurring compounds, such as plant metabolites, may be enough to ensure a good biodegradability for their eutectic mixtures too. It should be noted that these encouraging results have all been obtained in an aqueous medium, i.e., in the most relevant conditions in the context of a possible industrial application of DESs. However, it would be interesting to investigate also the biodegradability in soil, another possible recipient of environmental pollution, as it was done for example for imidazolium-based ILs.²⁷ Lastly, the mere fact that DESs are easily metabolized by wastewater microorganisms may represent just a part of the issue, as the nature of the products of such mineralization should be taken into account too. Looking at ChCl/HBD_{1–6} DESs, for example, the common HBA, ChCl, would most certainly release chloride anions in solution, which may represent a concern for the aquatic environment.²⁸ On this regard, the chemical oxygen demand (COD, amount of oxygen needed to oxidize a given substance, including oxidizable inorganic matter), could be a better indicator than BOD. A complete picture of the environmental fate of DESs would therefore require the

investigation and monitoring of the nature, concentration, and speciation of all their biodegradation products.

4. FEEDSTOCKS

A typical sentence that one could frequently read in the introduction of papers on DESs is that they “come from (potentially) renewable sources”. This claim is rooted into the fact that the most commonly employed DESs’ components are commodity chemicals, which are (or could be) sourced from biorenewable feedstocks, through fermentation processes or direct extraction from biomass. While this statement is in principle correct, its current validity ought to be verified by considering the actual feedstocks that are employed to produce each precursor on an industrial scale. The aim of the present section is to provide a picture of which shade of the “potentially” renewable definition has been currently achieved for the seven DES components reported in Figure 1. This approach would help classify the different DESs according to their real or only foreseeable renewable features. For this purpose, the *Ullmann’s Encyclopedia of Industrial Chemistry* was used as a reference for the relevant commercial-scale processes, and it was compared with recent literature on the topic.

The HBA salt of choline chloride (ChCl) is already a significant example in this regard, since it is produced through the reaction of trimethylamine, hydrochloric acid, and ethylene oxide (represented in Figure 2).^{6a,29} Among the building

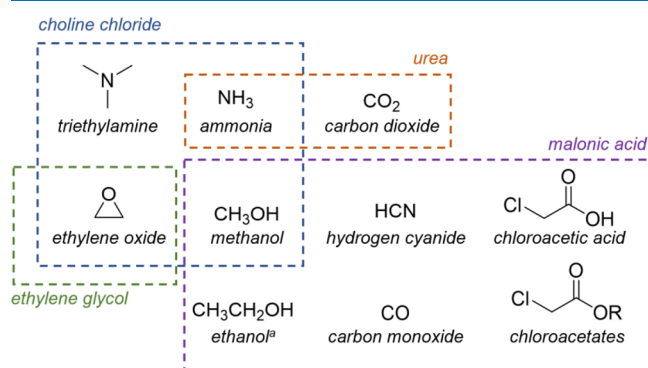


Figure 2. Fossil sources-derived chemicals involved in the industrial-scale production of the ChCl and HBDs. ^aEthanol should be excluded from this list when it is bioethanol.

blocks used in the chemical process, trimethylamine is produced from methanol and ammonia, which are actually derived from fossil sources, and the synthesis of ammonia is also particularly energy demanding; ethylene oxide comes from a renowned petrochemical derivative, ethylene,³⁰ but its synthesis from ethanol (and thus from renewable bioethanol) has also been proposed, as well as its replacement with glycolaldehyde.³¹ It should be pointed out that choline could theoretically be isolated from the different bioavailable sources (such as animal wastes, legumes...); yet, as far as we are aware, there are not scientific studies nor industrial processes dealing with its sustainable and/or cost-effective extraction. For these reasons, the renewable production of ChCl appears to be far from an actual implementation. Ethylene oxide is a substrate also for the industrial synthesis of HBD₂, ethylene glycol (EG).³² In the case of EG, however, alternative biosynthetic routes from sugars and lignocellulosic biomass have been developed, which appear to be promising: at present, efforts are being devoted to improve the efficiency of such processes,

in order to be economically competitive with the chemical synthesis, which means productivity (g/L/h), EG titer (g/L), and yield (g/g) values higher than 3.0 g/L/h, 100 g/L, and 0.5 g/g, respectively.³³ Recently, an engineered *Escherichia coli* strain has been employed at laboratory scale to obtain results as high as 2.25 g/L/h, 108 g/L, and 0.36 g/g, respectively.³⁴ EG may even be derived by HBD₁, glycerol (Gly),³⁵ which, despite being closely related to EG from a structural point of view, has a completely different sourcing. Indeed, Gly is the byproduct in the processes of hydrolysis or transesterification of triglycerides, among which the production of biodiesel is undoubtedly the most relevant, while the petrochemical synthesis from propylene has only seen some importance in the past century.³⁶ Gly can thus be considered as a biorenewable raw material, even if it is well-known that the crop-growing for the biodiesel industry poses sustainability issues related to soil exploitation and biodiversity; on this matter, an interesting alternative is represented by the use of microalgae as biomass for biodiesel (and Gly) production.³⁷ Another biorenewable HBD component is of course glucose (Glu), which is produced from starch via acid- or enzyme-catalyzed hydrolysis, the latter being the most relevant.³⁸ Conversely, the production of the HBD₃, urea (U), which is a major player in the fertilizer industry, depends on fossil sources: it is synthesized from ammonia (see above) and carbon dioxide, obtained during the process of ammonia synthesis.³⁹ Recent studies have shown that a viable alternative could be represented by the exploitation of biomass, in particular, urban waste, through gasification to syngas and further conversion into urea; however, this appears still far from a commercial application.⁴⁰

Finally, the two acids HBD₅₋₆, malonic acid and lactic acid, albeit structurally similar, are quite different from the point of view of renewability. Malonic acid (MA) is obtained from the hydrolysis of alkyl malonates, which derive from fossil sources. Indeed, they are produced either through the hydrogen cyanide process or the carbon monoxide process: in the first case, the building blocks are chloroacetic acid, hydrogen cyanide, and the appropriate alcohol, while the carbon monoxide process employs a chloroacetate, its corresponding alcohol and carbon monoxide (Figure 2).⁴¹ Alternative pathways may be represented by the thermocatalytic or enzymatic conversion of sugars and lignocellulosic biomass: on this matter, it should be noted that MA was inserted into the list of the top 30 value-added chemicals that can be produced from sugars, drawn up on behalf of the U.S. Department of Energy in 2004.⁴² Conversely, lactic acid (LA) has been predominantly obtained through fermentation processes, which also ensure a high degree of enantiomeric purity, since the 1990s.⁴³ Nowadays, scientific and technological advances in the biorenewable production of LA are focused on lowering the cost of the feedstock, by exploitation of lignocellulosic biomass or food waste instead of more expensive starch or refined sugars.⁴⁴

Some conclusions can be drawn from this brief survey. The first one is that, at the present time, no ChCl-based DES can be defined as totally renewable on a commercial scale, due to ChCl itself: indeed, several papers apply this definition, but they only justify it by the recyclability of the DES for its specific application, for a certain number of times, and by its biodegradability. Secondly, it is possible to sort ChCl/HBD₁₋₆ DESs into three “shades of renewability”, based on the different HBD components. This comparative classification

would see at the first place those HBDs whose production is currently detached from fossil sources, i.e., Gly, Glu, and LA, thus making their DESs the “most renewable” among those considered in this review. On the other hand, U seems the furthest one from a concrete renewable sourcing, while EG and MA stand in between, since they are not currently produced from biobased sources on a commercial scale, but the scientific progress on the matter appears to be in a more advanced state. It should also be considered that fermentation and biosynthetic pathways may afford the compounds of interest with lower purities compared to their chemical synthesis. For example, crude Gly produced from biodiesel industry has purities of 60–80%, and the price for refined Gly (96–99% or higher purity) fluctuated between 4 and 17 times higher than that for crude Gly, in the 2001–2009 period.⁴⁵ The issue on purity of DESs components is then articulated in two different questions. The first one concerns whether it would be possible to form the eutectic mixtures even with lower-grade components, compared to those usually employed in research laboratories, where DESs have been formed and studied up to now. Second, assuming that the first point can be fulfilled, it would be necessary to assess which applications of DESs are more sensitive to contamination in the components: for example, these would probably be less impacting when the eutectic mixture is employed in extractive or biomass treatment processes, while it can be envisaged that applications of DESs in fine organic synthesis, drug delivery, or electrochemistry would require high-purity solvent media. Thus, the evaluation of renewable source-derived HBA and HBD components cannot ignore the costs (and the environmental impact) associated with their possibly indispensable purification processes.

5. PRODUCTION

Alongside the renewability of their components, a notable feature that is often acknowledged to DESs is their cheap and environmentally friendly production. The claim is motivated both with the low cost of DESs components and the intrinsic simplicity of the eutectic mixture formation, since it involves the simple mixing of the components, through stirring at a suitable temperature, usually in the range 60–100 °C.⁴⁶ As mentioned in the previous chapter, ChCl and HBD₁₋₆ are commodity chemicals, produced in bulk by the petrochemical industry or from renewable sources, which would account for their low price. This aspect is particularly relevant in comparison with ILs, since the starting materials to produce the latter are usually specialty or fine chemicals, e.g. imidazole and alkyl iodides or bromides, for imidazole-based ILs. However, the actual cost is dramatically dependent on the required purity (as well as on the volumes involved) once more; therefore, a rigorous cost analysis should take into account the specific application for which the DES is intended. The aspects involved in the preparation of the DES from its components are most interesting because it is in principle very easy and intrinsically atom-economic. Compared to the synthesis of ILs, which generally involves alkylation reactions, performed in other solvents and in controlled atmosphere, with conventional workup and purification of the IL product, this represents a major improvement for what concerns sustainability. From an industrial point of view, however, the DES formation process is not trivial because of the issues related to the mixing of two solids, as well as to the handling of the viscous liquid produced. Furthermore, long heating times may

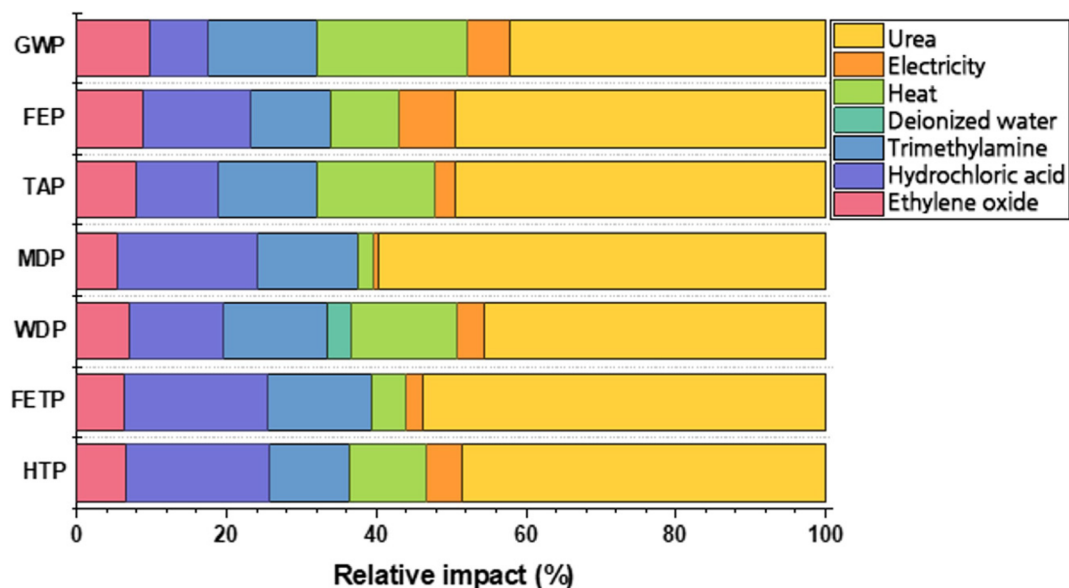


Figure 3. Different contributions, in the production of ChCl/U 1/2, to the seven indicators employed in the LCA study: GWP = global warming potential, FEP = freshwater eutrophication potential, TAP = terrestrial acidification potential, MDP = metal depletion potential, WDP = water depletion potential, FETP = freshwater ecotoxicity potential, HTP = human toxicity potential.⁴⁹ Adapted with permission from ref 49. Copyright 2022 The Royal Society of Chemistry.

result in partial decomposition of the DES components.⁴⁷ Mechanochemical synthesis, through twin screw extrusion technology, was proposed as a possible solution to these problems, affording ChCl/U 1/2 (and two other DESs) with high efficiency, avoiding prolonged exposition to high temperature, to dramatically reduce the thermal degradation.⁴⁸ The DES production through twin screw extrusion was recently taken as the reference method to analyze the environmental impact of ChCl/U 1/2 through cradle-to-gate (*i.e.*, from the raw materials to the finished product) life-cycle assessment (LCA).⁴⁹ The LCA approach considered both the synthesis of the components, ChCl and U, and the manufacturing of the eutectic mixture; seven indicators, including but not limited to the global warming potential or the water depletion potential, were used to compare the production of ChCl/U 1/2 with that of four VOCs, namely dichloromethane, ethyl acetate, methanol, and ethanol. The produced amount of the five solvents was normalized for a specific application, *i.e.*, the use as solvents for the synthesis of 0.2 kg of acetophenone through oxidation of 1-phenylethanol.⁴⁹ The study revealed that 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. Furthermore, the authors compared the production of 1 kg of ChCl/U 1/2 with 1 kg of other DESs, including ChCl/Gly, ChCl/EG, and ChCl/Glu, all in 1/2 molar ratio. The results showed that the different HBDs did not lead to dramatic changes in the output: with Gly, slightly higher global warming potential and terrestrial acidification potential were observed, this last indicator being higher than ChCl/U also for ChCl/Glu. Only in the case of water depletion potential, the value was significantly higher for ChCl/Gly, compared to the others. With EG as HBD, the results were substantially identical to ChCl/U.⁴⁹ An interesting outcome of the LCA study is that the feedstocks and the synthesis of the two components, ChCl and U, account for the

largest part of the burden on the seven indicators, as reported in Figure 3, while the actual production of the DES through mixing and heating impacts only to a limited extent. This provides a quantitative ground to the initial assumption that the preparation of DESs is simple and low-impacting, even at an industrial scale. In this framework, the environmental (and economical) impact of DESs production would be dumped mainly on the production of their components, thus orienting the direction for further improvement: indeed, increasing the environmental-friendly character of the synthesis of ChCl and HBDs would constitute a relevant part in addressing the whole issue. As shown by the LCA analysis, DESs production is already more desirable than that of two VOCs (at least for the specific application taken into account), but the target of overcoming also less impacting VOCs, such as methanol and ethanol, has not been met yet, and must be set in forthcoming development.

6. CONCLUSION

A comparative, broad-spectrum survey on the sustainability of widely employed DESs (or DES-like mixtures), sharing ChCl as their common HBA component, has been depicted. Four main aspects, *i.e.*, toxicity, biodegradability, renewable sourcing, and production have been considered and treated together for the first time, to provide a comprehensive outline. Toxicity and biodegradability have often been reported together (see references cited in Table 4); more in-depth analysis on the issues related to production has received attention only in recent times^{48,49} but assumptions on the renewability of DES components have never been tackled in detail. Overall, from our survey it appears that the “greenest” credentials could be attributed to ChCl/Gly mixtures, which show negligible toxicity and promising biodegradability profiles, together with current production of the HBD from renewable sources, even if the LCA gives a slightly worse outcome, compared to the others. On the other hand, ChCl/U DESs share with Gly-based ones good biodegradability and

appear even able to surpass them in terms of reduced toxicity and a more environmental-friendly production, at least as stated by the LCA; however, our aggregate evaluation is burdened, under a medium- and long-term sustainability point of view, by the negative impact of the current absence of feasible synthetic pathways for U from other resources than fossil fuels. Therefore, in our opinion these mixtures should be placed one step behind ChCl/Gly. Also ChCl/EG DESs display comparatively interesting results in terms of toxicity, biodegradability, and production, while their renewable sourcing at an industrial scale is not established yet, and could be regarded as a “yellow street light”. EG-based mixtures could then be considered similar to U-based ones in terms of sustainability, of course always keeping in mind the inherent hazard of EG as a pure component (see Table 1). Less information is available on ChCl/Glu mixtures, particularly concerning their toxicity toward animals, apart from the encouraging results on fish (Table 2). However, they are biodegradable according to the studies published so far, and the production of Glu from biomass is well established. On this basis, it would be desirable to have more insights into the toxicity of these mixtures, in order to properly compare them with so far best performing ChCl/Gly DESs. Lack of information also affects the evaluation of LA-based DESs, in which the HBD component is remarkably obtained from renewable sources, but surprisingly no studies on biodegradability or animal toxicity were found. On the other hand, the other carboxylic acid HBD considered, MA, was revealed to be less convincing than its competitors under all point of views: it was the only one to show some toxicity in the fish study (Table 2), it had worse biodegradability performances (Table 4), even if not bad in absolute terms, and its industrial production from renewable sources has not been achieved yet. Even if also in this case there is no sufficient available information to provide a complete assessment, ChCl/MA mixtures appear to be the less sustainable ones, among those here considered.

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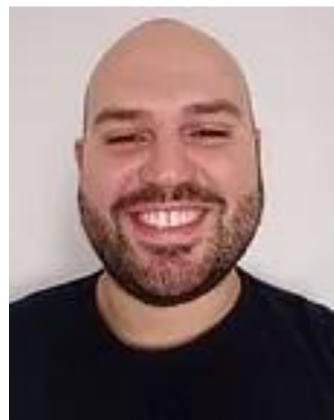
Notes

The authors declare no competing financial interest.

Biographies



Dr. Stefano Nejrotti graduated in Chemistry from the University of Torino, in 2017, after spending a research period at the IRCOF in Rouen (France). He obtained his PhD at the University of Torino in 2021, working on gold-catalyzed synthetic methodologies, and on synthesis in unconventional solvents. In 2019, he spent a period as visiting PhD student in the group of Prof. A. M. Echavarren at the ICIQ in Tarragona (Spain). He is currently a postdoctoral fellow at the University of Torino, where he works on the characterization of unconventional solvents, their use in organic synthesis, and on the synthesis of fluorescent molecules for applications in lighting.



Dr. Achille Antenucci obtained his PhD from Sapienza University of Rome in 2019, defending a thesis focused on Brønsted and Lewis acidic catalysts for organic synthesis. In 2018, he spent a period at the Max-Planck-Institut für Kohlenforschung (Mülheim an der Ruhr, Germany) as a visiting PhD student in the group of Prof. Benjamin List. Afterwards, he moved to University of Torino (Italy), where he worked for two years as a postdoctoral research fellow. Currently, he is working as a researcher in the chemical industry. His research interests rely on sustainable synthesis and catalysis, particularly focused on the exploitation of renewable feedstocks.



Dr. Carlotta Pontremoli obtained her PhD in Materials Science and Technology at Politecnico di Torino working on innovative nanomaterials based on Mesoporous Bioactive Glasses for smart release and tissue regeneration. During her PhD, she was involved in different European Projects giving her the possibility to spend a period as visiting PhD student at Universidad Complutense Madrid (Spain) in the group of Prof. Maria Vallet-Regí and at Charité – Universitätsmedizin Berlin (Germany). After her PhD, she moved to the University of Torino in the Department of Chemistry as a postdoc fellow, where her work is mainly related to the synthesis and characterization of NIR-photosensitizers for photodynamic therapy and the development of biocatalysts based on the bioconjugation of enzymes within innovative polymeric materials.



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