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Abstract

Nowadays there is a growing interest on the use of both lignocellulosic and algae biomass to produce biofuels (i.e. biohydrogen, ethanol and methane), as future alternatives to fossil fuels. In this purpose, thermal and thermo-chemical pretreatments have been widely investigated to overcome the natural physico-chemical barriers of such biomass and to enhance biofuel production from lignocellulosic residues and, more recently, marine biomass (i.e. macro and microalgae). However, the pretreatment technologies lead not only to the conversion of carbohydrate polymers (i.e. cellulose, hemicelluloses, starch and agar) to soluble monomeric sugar (i.e. xylose, glucose, arabinose and galactose), but also the generation of various by-products (i.e. furfural and 5-HMF). In the case of lignocellulosic residues, part of the lignin can also be degraded in lignin derived by-products, mainly composed of phenolic compounds. Although the negative impact of such by-products on ethanol production has been widely described in literature, studies on their impact on

biohydrogen and methane production operated with mixed cultures are still very limited.

This review aims to summarize and discuss literature data on the impact of pre-treatment by-products on H_2-producing dark fermentation and anaerobic digestion processes when using mixed cultures as inoculum. As a summary, furanic (5-HMF, furfural) and phenolic compounds were found to be stronger inhibitors of the microbial dark fermentation than the full anaerobic digestion process. Such observations can be explained by differences in process parameters: anaerobic digestion is performed with more complex mixed cultures, lower substrate/inoculum and by-products/inoculum ratios and longer batch incubation times than dark fermentation. Finally, it has been reported that, during dark fermentation process, the presence of by-products could lead to a metabolic shift from H_2-producing pathways (i.e. acetate and butyrate) to non-H_2-producing pathways (i.e. lactate, ethanol and propionate) and whatever the metabolic route, metabolites can be all further converted into methane, but at different rates.

Keywords

Anaerobic digestion; Biohydrogen; Dark fermentation; Furfural; 5-hydroxymethylfurfural; Thermo-chemical pretreatments; Vanillin

1. Introduction

Fossil fuels coming from coal, natural gas and petroleum represent about 80% of the primary energy resources consumed in the world, leading not only to their rapid depletion but also to many environmental damages, including global warming (Nigam and Singh, 2010; Saidur et al., 2011). Recently, the development of renewable energy sources has become a worldwide issue. Particularly, the production of second generation biofuels (i.e. bioethanol, biohydrogen and methane) through conversion of lignocellulosic substrates (i.e. agricultural residues, energy crops cultivated in no-arable lands and softwoods) has taken high consideration due to their composition rich in carbohydrates, their abundance, their renewability and they do not enter in competition with food feedstock (Mata-Alvarez et al., 2000; Mosier et al., 2005; Hendriks and Zemman, 2009; Monlau et al., 2013a). Even though, most of the research has focused so far on terrestrial biomass, the utilization of marine biomass such as micro and macro algae to produce so called "third" generation biofuels has gained a tremendous attention worldwide (Sialve et al., 2009; John et al., 2010; Ruiz et al., 2013; Chen et al., 2013; Prajapati et al., 2013).

Among renewable biofuels, biohydrogen and methane produced respectively by dark fermentation and anaerobic digestion (AD) when operated with mixed cultures, represent promising routes for the valorisation of lignocellulosic and algal biomass (Fig. 1). Anaerobic digestion is a process consisting in four physiological steps: hydrolysis, acidogenesis, acetogenesis and methanogenesis. During AD, the biomass is transformed into biogas, a mixture of methane (CH_4) and carbon dioxide (CO_2). The process can also be stopped at the acidogenic phase, so-called dark fermentation, where VFAs (Volatile Fatty Acids) and a biogas composed of a mixture of H_2 and CO_2 are produced concomitantly. To avoid the methanogenic step, the operational parameters in the reactor are fixed to inhibit methanogens, such as low pH, short hydraulic retention time and heat-shock pre-treatment of the inoculum (Nath and Das, 2004; Hawkes et al., 2007; Guo et al., 2010).

One major challenge in using lignocellulosic biomass is their native recalcitrant structure due to their natural physicochemical barriers, which inherently provide tensile strength and protection against pests and pathogens, but also confers a resistance to hydrolysis for further conversion by anaerobic fermentative

bacteria (Vancov et al., 2012; Monlau et al., 2012a). Carbohydrate compounds (i.e. cellulose and hemicelluloses) entrapped in the lignocellulosic matrix are associated in a complex and structured form presenting natural physico-chemical barrier properties that limit their hydrolysis and degradation during the fermentative processes (Taherzadeh and Karimi, 2008; Monlau et al., 2012a). The lignin composition and content as well as the degree of polymerization and crystallinity of cellulose, the structure of hemicelluloses, the pectin content, the accessible surface area and pore volume have been identified as the main parameters influencing the biodegradability (Taherzadeh and Karimi, 2008; Monlau et al., 2012a; Monlau et al., 2013a). Similarly, most of the algae species present a rigid cell wall conferring a resistance to bacterial attack and limiting their degradation during the anaerobic process (Ras et al., 2010; Gonzalez-Fernandez et al., 2011). To overcome these natural barriers, several types of pretreatment technologies commonly used for bioethanol production have been transferred with the purpose of increasing the biohydrogen and methane production from lignocellulosic residues and, more recently, from algal biomass too (Gonzalez-Fernandez et al., 2011; Monlau et al., 2013a; Sambusiti et al., 2013a). Among them, thermal and thermo-chemical pretreatments, which help mainly on solubilisation of carbohydrate polymers into soluble sugars (i.e. glucose, xylose, arabinose and galactose), have gained into considerable consideration, during the past five years (Panagiotopoulos et al., 2009; Hendriks and Zeeman, 2009; Park et al., 2013; Gonzalez Fernandez et al., 2011; Monlau et al., 2012b; Sambusiti et al., 2013a). Even if such pretreatments are often efficient in increasing the accessibility of biodegradable compounds to microorganisms by weakening the physicochemical barriers of the lignocellulosic biomass, they release also soluble sugars- derived by-products such as furfural, 5-HMF (hydroxylmethyl furfural), or lignin-derived by-products such as phenols, vanillin and syringaldehyde (Fox and Noike, 2004; Du et al., 2010; Monlau et al., 2012b; Sambusiti et al., 2013a). Recently, the release of furanic compounds in hydrolysates after thermal or thermo-chemical pretreatments of algal biomass was reported (Park et al., 2011a; Jung et al., 2011a,b; Park et al., 2013). Their concentration and nature in the hydrolysate depend on several factors such as mainly the biomass origin, the kind of pre-treatment and, the operating conditions, i.e. contact time, pH, pressure, temperature, concentrations and solid loading (Mussato and Roberto, 2004). The negative impact of such by-products was first reported by Mashevitskaya and Plevako (1938) who found that HMF interfered with the growth of the microorganism *Monilia murmanica*. Since, the presence of HMF has been reported as inhibitory of the

ethanol fermentation (Delgenès et al., 1996; Palmqvist and Hahn-Hägerdal, 2000), xylitol (Kelly et al., 2008), butanol production (Ezeji et al., 2007), enzymatic hydrolysis (Ximenes et al., 2010; Kim et al., 2011), biohydrogen production using pure cultures (Cao et al., 2009; Tai et al., 2010; Ho et al., 2010) and, more recently, in mixed cultures (Quémeneur et al., 2012). Overall, the inhibitory effect depends greatly of the type of microorganism and metabolism. In fact, Delgenes et al. (1996) studied the effect of six lignocellulosic degradation products (vanillin, furaldehyde, hydroxymethylfuraldehyde, hydroxybenzaldehyde and syringaldehyde) added separately on batch ethanol production using glucose-fermenting *Saccharomyces cerevisiae* yeast and *Zymomonas mobilis* bacteria and two xylose-fermenting yeasts *Pichia stipitis* and *Candida shehatae*. The glucose-fermenting yeast *S. cerevisiae* and xylose-fermenting yeasts *Candida shehatae* and *Pichia stipites* were very sensitive to the presence of inhibitors and were almost completely inhibited by furfural, HMF, syringaldehyde and vanillin concentrations at 2–5 g L^{-1}, whereas *Zymomonas mobilis* was found more resistant at such concentrations (Delgenès et al., 1996).

Due to their strong inhibitory effects on productivity and end-products formation, these by-products may constitute a limiting factor in the feasibility of using lignocellulosic materials for biotechnological conversion (Cao et al., 2009). To avoid the negative effect of such by-products on ethanol production, Almeida et al. (2009) proposed several processes for hydrolyzate detoxification, including evaporation, adsorption on active charcoal, adsorption on ion exchangers, solvent extraction, alkaline treatment or enzymatic treatment. However, detoxification methods increase significantly the overall costs due not only to capital and chemical costs, but also to the loss of sugars from primary material (Almeida et al., 2009). In an economic analysis of bioethanol production from willow hydrolyzate, Von Sivers et al. (1994) evaluated that the detoxification step contributed to 22% of the total cost production. Therefore, it is important to develop cheap and efficient methods for detoxification or to avoid the detoxification steps. For this purpose, it was envisaged to operate the anaerobic fermentative processes with mixed cultures, which seem to be more tolerant than ethanol-fermentative micro-organisms to these by-products. That represents a promising and sustainable alternative to produce energy from lignocellulosic and algal biomass hydrolysates without using any detoxification methods (Hendriks and Zeeman, 2009; Kaparaju et al., 2009; Monlau et al., 2012b). Torry-Smith et al. (2003) reported the implementation of an Upflow Anaerobic Sludge Blanket (UASB) reactor as purification step of bioethanol effluents to detoxify the process water for further reuse and, hence,

for reducing the overall production cost of the process. By using such technology, and besides the production of methane issued from the conversion of the residual COD, the inhibitory bioethanol by-products were also mainly consumed during the anaerobic process.

So far, several papers reviewed the effects of such by-products on ethanol production (Palmqvist and Hahn-Hägerdal, 2000; Klinke et al., 2004; Taherzadeh et al., 2007). However, to our knowledge, no paper summarized the effect of such by-products on anaerobic fermentative bioprocesses, operated with mixed cultures. The aim of this paper is to analyse and discuss the literature data on the effect of such by-products on biohydrogen and methane production operated with mixed cultures. First, the biochemical compositions of lignocellulosic and algal biomass are detailed and a brief description of the anaerobic fermentative processes (i.e. dark fermentation, anaerobic digestion) is made. Then, the nature of the by-products released in hydrolysates and the main factors influencing their release are reported and discussed. Finally, the impact of such by-products on both biohydrogen and methane production using mixed cultures is summarized.

2. Chemical composition of lignocellulosic and algal biomass

2.1.Lignocellulosic biomass

Lignocellulosic substrates are mainly composed of three types of polymers: cellulose, hemicelluloses and lignin along with smaller amounts of ash, pectins, proteins and soluble sugars (Jorgensen et al., 2007; Hendriks and Zeeman 2009). The composition of the three main fractions (cellulose, hemicelluloses and lignin) varies according to the type, variety, part and maturity of the plant (Mosier et al., 2005; Vanholme et al., 2010; Sambusiti et al., 2013b). Table 1 presents the compositions of the main biomass components, i.e. cellulose, hemicelluloses and lignin, encountered in the most common sources of lignocellulosic biomass. Hardwoods were not considered here due to their common conversion to energy by thermo-chemical processes, which differs from fuels produced biologically.

[Table 1. Chemical composition (i.e. cellulose, hemicelluloses and lignin) of various lignocellulosic

substrates expressed in terms of % Dry Matter (DM) (adapted and modified from Ruiz et al., 2013)]

The cellulose, as main structural constituent in plant cell walls, is a linear polysaccharide polymer of D-glucose subunits made of cellobiose units linked by β-(1→4) glycosidic bonds (Fengel and Wegener, 1984; Fengel, 1992). Cellulose in biomass is majorly in a form of well-organized crystalline structure and only in a small percentage as unorganized amorphous structure (Taherzadeh and Karimi, 2008). Cellulose is known to be more susceptible to microbial degradation in its amorphous form (Monlau et al., 2013a).

Hemicelluloses are composed of five-carbon (C_5) and six-carbon (C_6) sugars. The dominant sugars in hemicelluloses are mannose (C_6 sugar) in softwoods and xylose (C_5 sugar) in hardwoods and agriculture residues (Sun and Cheng, 2002; Emmel et al., 2003). Hemicelluloses also contain small amounts of acetyl groups (Kumar et al., 2009).

Finally, lignin is the third most abundant polymer in nature, after cellulose and hemicelluloses. Lignin is a main constituent of cell walls, providing to the plant its structural rigidity, impermeability and resistance against microbial attack and oxidative stress (Monlau et al., 2013a; Taherzadeh and Karimi, 2008). Three phenyl propionic alcohols exist as monomers of lignin: (i) coniferyl or guaiacyl alcohol (G), (ii) coumaryl or 4, hydroxycinnamyl alcohol (H) and (iii) sinapyl or syringyl alcohol (S). The nature and the quantity of lignin monomers (H, G and S) vary according to the plant species, its maturity and their spatial localization within the cells (Yoshizawa et al., 1993; Barakat et al., 2012). Lignin from softwoods (gymnosperms) contains mainly guaiacyl units, those from hardwoods (angiosperms) mainly guaiacyl and syringyl units, whereas the lignin from herbaceous plants (non-woody or graminae) contains all the three units (H, G, S) in significant amounts but at different ratios, G and S units being the main ones (Lapierre et al., 1986; Billa and Monties, 1995; Boerjan et al., 2003; Vanholme et al., 2010).

2.2.Algal biomass

Algal biomass has been recently investigated as a possible and complementary alternative to lignocellulosic substrates to produce biofuels, due to several advantages, such as (1) a higher productivity yields, (2) they do not require arable lands for growth and therefore do not outcompete food resources, (3) they can grow in a

variety of marine environments including fresh water, salt water and municipal wastewaters (Chisti et al., 2007; Sialve et al., 2009; Wei et al., 2013a). Commonly, algae are grouped in two main categories, ie. micro and macro algae, based on their morphology and size (John et al., 2011). Microalgae are microscopic photosynthetic organisms and mainly unicellular. In contrast, macroalgae are composed of multiple cells and organized in structure resembling to roots, stems and leaves of higher plants (Chisti et al., 2008; John et al., 2011). Macroalgae are classified into three categories ie. red, green and brown, according to the thallus color derived from the presence of natural pigments and different types of chlorophylls (Sze, 1993; Jung et al., 2011b; Park et al., 2011a). During their growth, algae can accumulate carbohydrates, lipids and proteins over a short time period (John et al., 2011). The proportion of the different components depends mainly to the environmental culture conditions such as irradiance, pH, temperature and nitrogen depletion (Chen et al., 2013). Table 2 shows the composition in terms of lipids, proteins and carbohydrates encountered in the most common sources of marine algae. Generally, macroalgae are characterized by lower contents of proteins and lipids but higher carbohydrates content compared to microalgae. Since carbohydrates are the precursors of furanic derivatives (i.e. furfural, 5-HMF) a special focus on their nature in both macroalgae and microalgae is made here below.

The carbohydrate composition in macroalgae depends mainly on their category: brown, red or green. The main carbohydrates in green algae correspond to mannan, ulvan, starch and cellulose (Jung et al., 2011b). In contrast, the main carbohydrates in brown algae are alginates, laminarin and mannitol, while red algae are mainly composed of cellulose, agarose, agaropectin and carrageenan (Whyte and Englar, 1981; Andrade et al., 2004; Park et al., 2011a; Park et al., 2013). Interestingly, some macroalgae strains such as *Saccharina japonica*, *Laminaria japonica* and *Gelidium amansii*, were reported to have carbohydrates content up to 50%, as shown in Table 2.

As shown also in Table 2, some microalgae strains present naturally high carbohydrate contents. Carbohydrates generally accumulate in plastids as reserve materials (i.e. starch), or are the main constituent of cell wall (Chen et al., 2013). Cell walls of microalgae consist of an inner cell wall layer and an outer cell wall layer and their composition varies from one species to another (Chen et al., 2013). The outer cell wall is generally composed of polysaccharides such as pectin, agar and alginate whereas the inner cell wall layer is mainly composed of cellulose (Yamada and Sakaguchi, 1982).

[Table 2. Chemical composition (i.e. lipids, proteins and carbohydrates) of various macro and micro algae expressed in terms of % DM.]

3. Anaerobic fermentative processes

In this section, a brief description of the dark fermentation and anaerobic digestion processes operated with mixed cultures is presented. In Figure 1, a conceptual scheme of the different steps occurring in dark fermentation and anaerobic digestion are represented. Here, only carbohydrate conversion was considered as such polymers are also precursors of furanic derivatives compounds from lignocellulosic and algal biomass.

[Fig. 1. Scheme of carbohydrate polymers degradation through dark fermentation and anaerobic digestion bioprocesses operated with mixed cultures (adapted from Monlau et al., 2013a)]

3.1.Dark fermentation

Biohydrogen can be produced by dark fermentation that constitutes an intermediate part of the full anaerobic digestion process, involving H2-producing fermentative bacteria and where the last methanogenic step does not occur. To avoid methanogenesis, pure cultures can also be used, but mostly mixed culture consortia are preferred since they are less expensive, easier to operate because of the absence of sterile conditions and convert a broader source of substrates (Ntaikou et al., 2010; Guo et al., 2010). Fermentative H_2-producing mixed cultures are easily sampled from natural environments, such as soils and anaerobic sludge to produce hydrogen (Ntaikou et al., 2010). One major disadvantage of using mixed cultures is the presence of no-hydrogen-producing microorganisms such as methanogens, homoacetogens, sulfate-reducing bacteria (SRB) and lactic acid bacteria (LAB). Furthermore, metabolism of these fermentative bacteria are involved in either a direct consumption of hydrogen or generate by-products such as propionate, ethanol and lactate that are produced through a zero-H_2 producing pathway (Guo et al., 2010; Ntaikou et al., 2010).

Among these no-hydrogen producing species, methanogens are considered as the main hydrogen-consuming microorganisms and can be deactivated in methanogenic inoculum by using several pretreatments such as heat shock, pH shock or addition of chemical inhibitors (i.e. bromoethanesulfonate, acetylene, inorganic acids and chloroform) (Guo et al., 2010; Chang et al., 2011a; Sarkar et al., 2013). Such inoculum pretreatments utilize the capacity of some acidogenic H_2-producing bacteria, ie. *Clostridi*um sp. to sporulate at high temperatures and germinate when the environmental conditions become favourable again while the non-spore-forming microorganisms i.e. methanogenic archaebacteria are eradicated (Lay et al., 2003; Fang et al., 2006; Argun et al., 2008).

There are two common pathways in the production of biohydrogen by dark fermentation: one producing acetate and the second butyrate, as shown in Fig 1. Theoretically, 4 mol of hydrogen can be produced from glucose through the acetate pathway and 2 mol through the butyrate pathway (Antonopoulou et al., 2006). When using mixed cultures, metabolic pathways are more variable in regards to the composition and structure of the microbial community, the type and concentration of substrates and the operating conditions. Hawkes et al. (2007) suggested an average theoretical pathway for mixed cultures leading to 2.5 mol H_2 mol^{-1} hexose and a ratio of butyrate/acetate of 3:2. However, recent studies showed that acetate accumulation and consequently butyrate/acetate ratio do not correlate with biohydrogen production and only the amount of easily accessible sugars can predict the amount of biohydrogen that can be produced (Monlau et al., 2012a; Guo et al., 2013).

3.2.Anaerobic digestion

Anaerobic digestion corresponds to a full microbiological degradation process under anaerobic conditions leading to stabilization of organic matter and the formation of a biogas composed mainly of CH_4 (55-75%) and CO_2 (25-45%). Commonly, mixed consortia used for anaerobic digestion include a large range of inoculum, such as municipal anaerobic digested sludge, rumen liquor from cattle, digestate from agricultural anaerobic digestion plant and organic fraction from municipal solid wastes.

Microbial ecology in anaerobic digestion is complex and involves several microbial groups at each step of the process. Anaerobic digestion is generally divided into four main steps, so-called hydrolysis, acidogenesis,

acetogenesis and methanogenesis (Fig. 1). During the hydrolysis step, organic polymers, such as carbohydrates, are hydrolysed into simple sugars monomers. Hydrolytic bacteria, known as primary fermenting bacteria, are facultative anaerobes and hydrolyse the substrate with extracellular enzymes. A wide range of enzymes, i.e. cellulases, hemicellulases, proteases, amylases and lipases, can be produced at this stage (Taherzadeh and Karimi, 2008). When microorganisms produce suitable enzymes, hydrolysis is a relatively fast step. In contrast, if the substrate is not fully accessible to enzymes, as in the case of lignocellulosic substrates, hydrolysis becomes the rate-limiting step (Taherzadeh and Karimi, 2008). During acidogenesis, primary fermentative bacteria convert hydrolysis products to a biogas composed of CO_2 and H_2 and to microbial metabolites including volatile fatty acids, ie. acetate, propionate, butyrate and valerate, other acids, such as lactate, succinate and alcohols, ie. ethanol, butanol, acetone. Acidogenic bacteria are able to metabolise organic compounds at very low pH around 4. Methanogenic microorganisms cannot use directly all products from the acidogenic step. Except for acetate, H_2 and CO_2, they have to be further transformed, during a so-called acetogenic phase, to acetate, hydrogen and carbon dioxide by secondary fermenting bacteria, also called Obligate Hydrogen-Producing Bacteria (OHPB). However, thermodynamics of these reactions are unfavourable and these microorganisms can only live in syntrophy with end-product users, ie. methanogens. Indeed, the methanogenic step corresponds to the final conversion of acetate, carbon dioxide (CO_2) and hydrogen (H_2) into a biogas which is composed mainly of CH_4, (55-75%) and CO_2 (25-45%). Methanogenic microorganisms involved are obligate anaerobic archaea and two groups of methanogens are mainly distinguished, the hydrogenotrophic and acetoclastic methanogens, which transform the mixture CO_2/H_2 and acetate into methane, respectively. Hydrogenotrophic microorganisms convert H_2 and CO_2 produced by fermentative bacteria into CH_4, keeping a low hydrogen partial pressure and thus supporting the growth of acetogenic bacteria. The relative abundance of hydrogenotrophs and acetotrophs are variable according to environmental factors (e.g. acetate, ammonia, hydrogen and hydrogen sulphide concentrations) and operating conditions (e.g. Hydraulic Retention Time, pH, type of substrate and source of inoculum) (Demirel and Scherer, 2008) as well as solid contents (Abbassi-Guendouz et al., 2013). During start-up of anaerobic digesters, it was reported that hydrogenotrophic methanogens (e.g. *Methanoculleus*, *Methanobacterium*) are first dominant with a subsequent decrease of the H_2 concentration and, after stabilization of the process, a shift to acetoclastic methanogens (e.g. *Methanosarcina*, *Methanosaeta*) occurs

(Illmer et al., 2014; Demirel and Scherer, 2008).

Furthermore, high levels of ammonia favour the dominance of hydrogenotrophic methanogens in mesophilic anaerobic digestors (Krakat et al., 2010; Kampmann et al., 2012). Approximately 65-70% of the methane produced in anaerobic digesters comes from acetate, when acetotrophic methanogens are dominant, otherwise, in absence of acetoclastic methanogens such as *Methanosaeta* sp., acetate oxidation to H_2 and CO_2 is the main dominant pathway (Karakashev et al., 2006).

4. By-products from algae and lignocellulosic biomass hydrolyzate

4.1.Nature of by-products

To overcome natural physico-chemical barriers of lignocellulosic and algae biomass, a pretreatment step is generally applied prior to anaerobic fermentation (Jung et al., 2011a,b; Ruiz et al., 2013; Gonzalez-Fernandez et al., 2012a,b). Generally, pretreatment methods are divided into three main categories: physical, thermo-chemical and biological processes as well as a combination of these (Mosier et al., 2005). Among them, thermal and thermo-chemical pretreatments have been widely investigated to overcome the physico-chemical barriers of lignocellulosic biomass and algae to enhance biofuel production (Taherzadeh and Karimi, 2008; Gonzalez-Fernandez et al., 2012b; Ruiz et al., 2013; Monlau et al., 2013a; Sambusiti et al., 2013a). Besides solubilisation of carbohydrate polymers into soluble sugars (mainly glucose, xylose and arabinose), they also lead to the generation of derived lignocellulosic by-products as shown in Fig. 2 (Palmqvist and Hahn-Hägerdal, 2000; Mussato and Roberto, 2004; Jonsson et al., 2013). These by-products are generally divided into three groups: furans, weak acids and phenolic compounds.

Furanic compounds such as furfural and 5-HMF originate from the dehydration of pentose and hexose simple sugars, respectively. A recent study reviewed the different routes of furfural and HMF formation from simple sugars. At least four routes for the formation of HMF from glucose and three routes for furfural formation from xylose were identified (Rasmussen et al., 2013).

Phenolic compounds, such as vanillin and syringaldehyde, are generated from the degradation of syringyl (S) and guaïacyl (G) units of lignin polymers, respectively (Barakat et al., 2012). Recent findings showed that biomass monomeric sugars can further react to form pseudo-lignin compounds when exposed to severe

pretreatments conditions (Sannigrahi et al., 2011). This phenomenon results in an increase of the acid insoluble Klason lignin content. Hu et al. (2012) observed also the generation of pseudo-lignin compounds during dilute-acid pretreatment of hybrid poplar. They suggested that 3,8-dihydroxy-2-methylchromone and 1,2,4-benzenetriol derived from furfural and 5-HMF, respectively, were the key intermediates of pseudo-lignin formation during polymerisation and/or condensation reactions.

Lignocellulosic hydrolyzates contain also weak acids mainly acetate, formic acid and levulinic acid (Jonsson et al., 2013). Palmqvist and Hahn-Hägerdal (2000) reported that furfural and 5-HMF can be indeed degraded into weak acids (i.e. formic acid and levulinic acid) under very strong pretreatment conditions (i.e. high acidity and/or high temperature). Acetate is generated after hydrolysis of hemicellulose acetyl groups during thermal and thermo-chemical pretreatments (Panagiotopoulos et al., 2011).

[Fig. 2. Global scheme of by-products generation (i.e. aliphatic acids, furanic derivatives and phenolic compounds) after thermal and thermo-chemical pretreatments of lignocellulosic and algal biomass]

4.2.Factors influencing the release of by-products

The presence of derived lignocellulosic by-products was reported previously after various types of pretreatment of lignocellulosic materials, such as microwaves (Jackowiak et al., 2010), steam explosion (Cantarella et al., 2004; Badshah et al., 2012a; Di Girolamo et al., 2013), liquid hot water (Kaparaju et al., 2009; Monlau et al., 2012b; Sambusiti et al., 2013a), subcritical water (Fox et al., 2003), wet oxidation (Klinke et al., 2002; Fox and Noike, 2004; Du et al., 2010) or thermo-chemical pretreatments (Fox et al., 2003; Du et al., 2010; Larsson et al., 1999; Monlau et al., 2012b). In Table 3, the effects of various thermal and thermo-chemical pretreatments on the release of the most commonly found by-products (i.e. furfural, 5-HMF, phenol, acetate and formic acid) in lignocellulosic hydrolyzates are summarized. The composition in by-products (Tab. 3) depends mainly on the type of biomass as well as on the nature and severity of the pretreatment (Mussato and Roberto, 2004; Panagiotopoulos et al., 2011). The by-products listed here are not exhaustive since, in a recent study, Du et al. (2010) reported 40 potential inhibitory by-products generated

during various thermal and thermo-chemical pretreatments of different lignocellulosic biomass. Furfural and 5-HMF are mostly formed at low pH (i.e. thermal and thermo-acid pre-treatment) and generally negligible at high pH (i.e. thermo-alkaline pre-treatment) (Du et al., 2010; Monlau et al., 2012b). In contrast, at high pH, phenolic compounds are preponderant because such pre-treatment has mainly an effect on lignin degradation (Taherzadeh and Karimi, 2008; Monlau et al., 2012b; Naseeruddin et al. 2013).

Recently, Panagiotopoulos et al. (2011) found that the ratio ∑ (soluble sugars) / ∑ (inhibitors) can be used as a good tool for assessing the suitability of a hydrolyzate to be further fermented (Tab. 3). As the ratio ∑ (soluble sugars) / ∑ (inhibitors) depends not only on the nature of the biomass but also on pretreatment severity (temperature, residence time and chemical concentration), a severity factor (R_0) and a combined severity factor (CS) were proposed to compare thermal and thermo-chemical pretreatments, respectively (Panagiotopoulos et al., 2011, Pedersen and Meyer, 2010). Severity factor Ro is used to compare results of thermal pretreatments carried out at different temperature and time conditions (Ruiz et al., 2013; Overend and Chornet, 1987). The R_0 severity factor is generally expressed using a Log function as shown in Equation 1.

$$\text{Log } R_0 = \text{Log } [t \exp [(T-100)]/14.75] \quad (1)$$

where t corresponds to reaction time (min), T is the temperature (°C), 100 is the temperature of reference and 14.75 is an empirical parameter related with activation energy, assuming pseudo first order kinetics. The results are usually represented as a function of log (R_0).

A combined severity (CS) factor taking into account the pH value of the liquor after dilute-acid pretreatment was proposed to consider additional effect of the acid catalyst (Abatzoglou et al., 1992; Larsson et al., 1999; Panagiotopoulos et al., 2011; Di Girolamo et al., 2013; Park et al., 2013). The combined severity factor is defined in Equation 2

$$CS = \log (R_0) - pH \quad (2)$$

However, such equations did not consider the effect of pH variation, which increases during thermo-alkaline pretreatment. For this reason a combined severity (CS_2) factor was proposed (Pedersen and Meyer, 2010). The severity of the pretreatment procedure at basic pH values can here be easily compared by using Equation (3) (Pedersen and Meyer, 2010)

$$CS_2=\log(R_0) + |pH-7| \quad (3)$$

Recently, the use of thermal and thermo-chemical pretreatments on algal biomass (i.e. microalgae, macroalgae) or lipid extracted algae residues were reported and an increase of anaerobic fermentation performances was shown (Jung et al., 2011a,b; Gonzalez-Fernandez et al., 2012a,b; Ruiz et al., 2013; Keymer et al., 2013). However, the lack of lignin in algal biomass makes simpler the use of pre-treatments and the conditions required for the solubilization of carbohydrate polymers are less drastic than those used with lignocellulosic residues (Ruiz et al., 2013). Nonetheless, generation of furan derivatives (i.e. furfural and 5-HMF) was reported in algae biomass hydrolyzates likely by degradation of the carbohydrate polymers such as cellulose, starch, agar and alginate compounds (Fig. 2 and Table 3) (Jung et al., 2011a,b; Park et al., 2011a; Yun et al., 2013; Chen et al., 2013). Jung et al. (2011b) reported furfural contents ranging from 1.79 g L^{-1} to 4.84 g L^{-1} after thermal pre-treatment of the brown macroalgae *L. Japonica* at 170°C during 5 and 40 min respectively. Jung et al. (2011a) reported 5-HMF concentrations ranging from 2 g L^{-1} to 8 g L^{-1} after thermo dilute-acid pre-treatment of *S. japonica*. Consistently, Yun et al. (2013) reported 5-HMF generation between 0.2 g L^{-1} and 4.3 g L^{-1} after dilute acid pre-treatment of the microalgae *C. vulgaris*.

[Table 3. Composition of various hydrolyzates issued from algae and lignocellulosic biomass in terms of soluble carbohydrates and by-products generation.]

5. Effect of by-products on biological anaerobic process using mixed cultures

Furanic and phenolic compounds were reported to inhibit enzymatic hydrolysis of various fermentative

bacteria in pure-culture bioprocesses operated for ethanol, biohydrogen, xylitol, butanol and lipid production (Delgenès et al., 1996; Ezeji et al., 2007; Kelly et al., 2008; Cao et al., 2009; Ho et al., 2010; Ximenes et al., 2010). The effect of weak acid mainly acetate derived from acetyl groups of hemicelluloses, which was already reported to have a negative effect on ethanol fermentation, will not be discussed here. Indeed, acetate is a metabolic intermediate of anaerobic digestion and higher concentration of acetate than generally reported in lignocellulosic hydrolyzates can be easily tolerated by anaerobic consortia. Concerning biohydrogen production through dark fermentation, until now no work reported the effect of initial acetate addition on dark fermentation process operated with mixed cultures. Nevertheless, acetate was not reported to inhibit specifically and significantly the growth of pure clostridial species involved in hydrogen production (Ezeji et al., 2007; Cao et al., 2009).

5.1.Main modes of action of by-products on microorganisms

Furanic compounds (i.e. furfural and 5-HMF) are known to have detrimental effects on microorganisms by inhibiting cell growth, induce DNA damage and inhibit several enzymes of the glycolysis pathway (Palmqvist and Hahn-Hägerdal, 2000; Almeida et al., 2009). Phenolic compounds damage microbial cells by altering selectively the membrane permeability, causing leakage of intracellular components and inactivation of essential enzymatic systems (Heipieper et al., 1994; Palmqvist and Hahn-Hägerdal, 2000; Campos et al., 2009; Hierholtzer et al., 2013). Low molecular weight phenolic compounds are considered as the most toxic compounds to microorganisms than high molecular weight ones (Klinke et al., 2004). In *E. coli*, phenolic compounds were found to be more toxic than furans (Mills et al., 2009). Both furans and phenols generate *Reactive Oxygen Species* (ROS) (i.e. H_2O_2, O_2^- and OH^-) that impact cell metabolism and induce apoptosis (Ibraheem and Nnimba, 2013). The individual effects of toxics on microbial cells are related to their structure and hydrophobicity. These characteristics determine the intrinsic ability of these compounds to penetrate cell membranes and cause cellular disturbances. High hydrophobic compounds are indeed suspected to affect cell membrane transporters and therefore compromise membrane integrity (Mills et al., 2009).

Microorganisms differ in their ability to adapt and grow in presence of toxic compounds and can use different adaptation mechanisms to avoid or repair damages caused by these toxics. Molecular adaptation mechanisms and activities of some bacterial species in response to lignocellulose-derived inhibitory compounds were recently reviewed (Lee et al., 2012; Ibraheem and Nnimba, 2013). In order to maintain the integrity of the cell membrane, some bacterial species may respond to the presence of toxic compounds by converting the cis-unsaturated fatty acids to trans-unsaturated ones at the cell membrane level (Heipieper et al., 1994; Palmqvist and Hahn-Hägerdal, 2000). Recently, variations in effect of inhibitory by-products on bacteria was also attributed to differences in cell surface structures between Gram-negative and Gram-positive species, but the effect observed was mainly species-dependent (Cueva et al., 2012). To better tolerate the stress generated by inhibitory by-products, some bacteria produce stress response proteins such as SOS response proteins and heat shock proteins, which repair the damaged DNA and maintain the structure of the enzymatic systems (Ibraheem and Nnimba, 2013). Some other microorganisms, mostly aerobic Gram-negative bacteria, can directly transform and/or degrade the furanic compounds, by utilizing them as a carbon source (Almeida et al., 2009; Wierckx et al., 2011). In particular, Furfural degradation proceeds via 2-furoic acid, which is metabolized to the primary intermediate 2-oxoglutarate. HMF is converted, via 2,5-furandicarboxylic acid, into 2-furoic acid (Almeida et al., 2009). Under anaerobic conditions, some bacteria (e.g., *Escherichia coli*, *Clostridium acetolyticum)* can convert furfural and 5-HMF to less inhibitory furfuryl compounds and HMF alcohols (Zaldivar et al., 1999; Zhang et al., 2012). As an illustration, in *Escherichia coli* LYO1, furfural is converted more rapidly than 5-HMF and, since it is more toxic than 5-HMF, this selective transformation is beneficial for cell growth (Zaldivar et al., 1999).

5.2.Effect of by-products on dark fermentation process operated with mixed cultures

5.2.1. Effect on dark fermentation

Table 4 summarizes the main results published in literature on the impact of furanic and phenolic compounds added separately or in combination (hydrolyzate) on dark fermentation process performances operated with mixed cultures. At a concentration of 1 g L^{-1}, Quéméneur et al. (2012) showed that furanic (furfural and 5-HMF) and phenolic compounds added separately decreased the hydrogen yield from xylose but did not lead

to total inhibition. Increasing the 5-HMF concentration at around 1.5-2 g L^{-1} showed a severe decrease of hydrogen production down to zero (Park et al., 2011a). Among the by-products investigated, phenolic compounds (i.e. phenols, syringaldehyde and vanillin) were found to have less impact on hydrogen production than furanic compounds. The addition of 1 g L^{-1} of furan derivatives led to a reduction of the hydrogen yield of 68 % (furfural) and 76 % (5-HMF) compared to the control (Quéméneur et al., 2012). The effects of such by-products was also investigated using hydrogen-producing bacteria in pure cultures and similar trends to that in mixed cultures were reported (Cao et al., 2009; Ho et al., 2010; Tai et al., 2010). Indeed, total inhibition of hydrogen production in *Thermoanaerobacterium thermosaccharolyticum* was reported in presence of 1.8 g L^{-1} of 5-HMF or 2 g L^{-1} of furfural (Cao et al., 2009). *Clostridium butyricum* yielded H_2 at approximately 1.4 mol H_2 mol^{-1} glucose in presence of 200–400 mg L^{-1} phenol, but significant inhibition of cell metabolism was observed at phenol concentration higher than 1000 mg L^{-1} with total hydrogen pathway inhibition at concentrations higher than 1.5 g L^{-1} (Tai et al., 2010).

As shown in Table 4, the inhibition of hydrogen-producing mixed-cultures was reported with thermal or thermo-chemical hydrolyzates containing a mixture of by-products (Chang et al., 2011b; Monlau et al., 2013b; Park et al., 2011a). Interestingly, Jung et al. (2011a) showed an inverse relationship (R^2=0.84) between the 5-HMF content and hydrogen yields. Chang et al. (2011b) reported no hydrogen production after ten days from various dilute acid rice straw hydrolyzates, mainly due to the presence of by-products (i.e. furfural and 5-HMF). Indeed, by removing furfural and 5-HMF from the hydrolyzate, hydrogen was produced significantly. In addition, Monlau et al. (2013b) reported a total inhibition of fermentative hydrogen production after supplementation of the culture medium with 15 % (v/v) of dilute-acid sunflower stalk hydrolysate, corresponding to 172 mg L^{-1} of furfural, 19 mg L^{-1} of 5-HMF and 3 mg L^{-1} of total phenolic compounds. Surprisingly, when the compounds were added separately at much higher amount of 1 g L^{-1} and under the same conditions, biohydrogen production was negatively affected but was not totally inhibited (Quéméneur et al., 2012). These observations suggest either the presence of other unknown inhibitors in hydrolyzates and/or a synergistic effect of the different by-products as their level of inhibition was much lower than when used separately (Quéméneur et al., 2012; Monlau et al., 2013b). Such synergy effect of by-products (furfural, 5-HMF, phenolic compounds) was previously reported on bioethanol fermentation by *Saccharomyces cerevisiae*, on biohydrogen production by *T. thermosaccharolyticum* and

lipid production by the oleaginous yeast *Rhodosporidium Toruloides* (Larsson et al., 1999; Mussatto and Roberto, 2004; Cao et al., 2009).

Additionnally, the presence of by-products led also to an increase of lag-phase in dark fermentation, showing the necessity of microorganisms to adapt (Kongjan et al., 2010; Quéméneur et al., 2012). Datar et al. (2007) reported that, when steam exploded corn stover hydrolyzate (200°C for 1 min) was treated with activated charcoal to remove inhibitory by-products, the hydrogen yield remained the same, but the lag phase decreased from 24 h to about 12 h suggesting a shorter adaptation time of microorganisms in absence of by-products. By using unadapted anaerobic mixed-cultures, Quéméneur et al., (2012) reported that the highest increase in lag-phase was observed with phenol, followed by furfural, vanillin, 5-HMF and syringaldehyde at 1 g L^{-1}. In particular, the lag-phase increased dramatically from 3 days to 23 days in presence of phenolic compounds (Quéméneur et al., 2012). Mainly, a negative correlation was observed between lag phase and molecular weight of furanic and phenolic compounds (Quéméneur et al., 2012). For instance, furans having molecular weight of 96 g mol^{-1} (furfurals) and 126 g mol^{-1} (5-HMF) exhibited a lag phase twice longer with furfurals than HMF-added cultures. Such differences can be explained by the intrinsic ability of these compounds to penetrate cell membranes: the higher the molecular mass, the slower was the penetration into a cell and the shorter the lag phase (Quéméneur et al., 2012).

5.2.2. Effect of by-products on fermentative metabolic pathways and microbial communities

In the case of mixed cultures, furans and phenolic compounds may selectively affect the growth of individual species within the microbial consortium. Consequently, they may influence both metabolic pathways and bacterial population dynamics. Few studies investigated metabolic pathway and microbial community changes in presence of such by-products during dark fermentation (Konjan et al., 2010; Park et al., 2011a; Quéméneur et al., 2012).

Quéméneur et al., (2012) reported acetate and butyrate as major metabolites in the soluble fraction associated with hydrogen production when using glucose as control. Significant changes in metabolic profiles were observed, depending on the nature of the inhibitory by-products added in the medium (i.e. furfural, 5-HMF,

phenols, vanillin and syringaldehyde). Nevertheless, and whatever the inhibitor supplemented, the mixed-culture was dominated by *Clostridium* spp., especially *C. beijerinkii* more resistant to inhibitors and, thus, it can be considered as an ideal candidate for H_2 production from lignocellulosic hydrolyzates (Quéméneur et al., 2012). In contrast, the relative abundance of efficient hydrogen-producing bacteria *C. acetobutylicum* and *C. pasteurianum* were drastically affected by furanic and phenolic compounds (Quéméneur et al., 2012). In presence of such by-products, the emergence of competitive none-H_2 producing bacteria such as *C. cellulosi* and *Sporolactobacillus sp.* was observed (Quéméneur et al., 2012).

Interestingly, inhibition of biohydrogen production in presence of by-products does not mean the absence of bacterial activities since carbohydrates can be degraded through none-hydrogen-producing pathways such as lactacte, ethanol and propionate pathways (Konjan et al., 2010; Park et al., 2011a; Quéméneur et al., 2012; Monlau et al., 2013b). That suggests that H_2-producing bacteria are more sensitive to the presence of by-products than other microorganisms. Furthermore, Park et al. (2011a) reported that when 1.5 g L^{-1} of 5-HMF was added to a galactose medium, no hydrogen was produced but propionate and mainly lactate were generated from carbohydrates through competing H_2 pathways (Park et al., 2011a). Similarly, Monlau et al., (2013b) observed a decrease in biohydrogen production from glucose by adding increasing volumes of dilute-acid sunflower stalk hydrolyzates containing by-products. In that case, for a volume lower than 7.5 % (v/v), corresponding to concentration in fermenter of 86.2 mg L^{-1} of furfural, 9.5 mg L^{-1} of 5-HMF and 1.5 mg L^{-1} of phenolic compounds, no hydrogen inhibition was observed and acetate and butyrate were the main metabolites produced concomitantly with hydrogen. *Clostridium* genus, which plays a key role in fermentative mixed cultures producing H_2, was found to be dominant (Monlau et al., 2013b). In contrast, at a volume higher or equal to 15 % (v/v), no hydrogen production was reported and this inhibition was accompanied to a shift from hydrogen-producing pathways (i.e. acetate/butyrate) to non-hydrogen-producing pathways (i.e. lactate/ethanol). Production of ethanol and lactate involved in zero-hydrogen balance pathways was also concomitant with a population shift from *Clostridium sp.* to *Sporolactobacillus sp.*

The inhibitory effect is strongly dependent of the initial adaptation of the initial microbial ecosystems. Kongjan et al. (2010) showed that 5-HMF and furfural at low concentration of 50 and 24 mg L^{-1}, respectively, were efficiently removed in a CSTR reactor using adapted hyperthermophilic microbial culture. Both furfural and 5-HMF can be transformed into less inhibitory furfuryl and HMF alcohols and then be

degraded by clostridial species and facultative anaerobes (Zhang et al., 2012; Wierckx et al., 2011). At low concentrations, phenols were also reported to be degraded by many clostridial species generally involved in hydrogen production (Tai et al., 2010). Contrarily, Quéméneur et al. (2012) showed that no gas was produced during dark fermentation of inhibitor compounds such as furfural, 5-HMF, vanillin and syringaldehyde, as sole carbon source and at an initial concentration of 1g L^{-1}. It is clear that the efficiency of H_2 production using mixed cultures is dependent on nature and concentration of toxic compounds but more investigations are still required to determine the exact impact of the origin of mixed cultures as well as the most adapted microbial community structures. Nonetheless, the presence of by-products during dark fermentation using mixed cultures may favour the production of other carboxylates (i.e. lactate and propionate) or biofuels (ethanol). However, supplementary investigations are needed to support this assumption. Recent advances in molecular techniques, such as functional community fingerprinting (Quéméneur et al., 2011), functional genomics (e.g., detection of genes related to the resistance or the degradation of the by-products) (Endo et al., 2008) and metagenomics (Chistoserdova, 2010), would be particularly applicable when combined to the analysis and monitoring of fermentative mixed cultures exposed to by-products, for better understanding of their influence on metabolic pathways and regulatory networks.

[Table 4. Summary of the impact of by-products released during thermal and thermo-chemical pretreatments on dark fermentative biohydrogen production using mixed cultures as inoculum]

5.3.Effect on anaerobic digestion (AD)

5.3.1. Effect of individual by-products on AD

Table 5 shows the main data published about the impact of furanic and phenolic compounds on anaerobic digestion. The effects of such by-products were investigated on simple substrates (i.e. xylose, acetate and propionate) as well as more complex substrates (i.e. cellulose), allowing to have a global vision on their effect on the overall process.

At a concentration of 1 g L^{-1}, furanic compounds (i.e. 5-HMF and furfural) added to a growth medium

containing xylose at 1 g/L did not reduce the methane yield (Barakat et al. 2012). Badshah et al. (2012b) investigated the degradation of cellulose during anaerobic digestion by adding separately various concentrations of furfural (1, 2 and 4 g L^{-1}) and 5-HMF (1, 3 and 6 g L^{-1}). At concentrations of 1 and 2 g L^{-1} of furfural and 1 and 3 g L^{-1} of 5-HMF, no methane production inhibition was observed. At 4 g $L^{-1}$of furfural, a moderate accumulation of acetate and propionate was found at the end of experiment (55 days) suggesting a partial inhibition of the methanogenic activity and likely no inhibition of hydrolysis and acidogenesis steps. At 6 g L^{-1} of 5-HMF, no biogas was produced suggesting that 5-HMF caused a total inhibition of AD. After 55 days of incubation, accumulation of fermentative metabolites in the liquid phase was found with mainly acetate (1 g L^{-1}) and propionate (0.09 g L^{-1}). This result suggest that methanogenesis was severely impacted (Badshah et al., 2012b). Furthermore, total amounts of metabolic intermediates such VFAs, soluble sugars and methane were lower than if complete conversion of cellulose occurred, suggesting that hydrolysis was also severely affected at such concentration of 5-HMF (Badshah et al., 2012b). Methanogenic activity from acetate and propionate was also investigated at several concentration levels of 5-HMF (Park et al. 2011b). Consistently, Park et al. (2011b) showed that the degradation of acetate is possible up to 5 g $L^{-1}$of 5-HMF, but a total inhibition of the methanogenic activity occurred at a concentration of 10 g L^{-1}.

Regarding the degradation of lignin-derived by-products, phenolic compounds such as phenol, vanillin and syringaldehyde were added at a concentration of 1 g L^{-1} to xylose at 1 g L^{-1} and the final methane yields were not reduced (Barakat et al. 2012). Chapleur et al. (2013) investigated the effect of increasing phenol concentrations on the anaerobic degradation of cellulose. The archaeal methanogenic and fermentative bacterial activities were inhibited at a threshold value of 1.5 g L^{-1} and 2 g L^{-1} of phenol, respectively (Chapleur et al., 2013). Similarly, Fedorak and Hrudey (1984) reported that methanogenic activity of anaerobic sludge was not affected at concentrations lower than 1.2 g L^{-1} of phenols, since acetate and propionate were fully degraded into methane. When phenol concentration exceeded 1.2 g L^{-1}, total methane production decreased sharply (Fedorak and Hrudey, 1984). Kayembe et al. (2013) showed a negative linear correlation between the toxicity of phenolic compounds and their hydrophobic properties. An increase in the number of hydroxyl groups on aromatic compounds was indeed associated with a decrease of the compound toxicity on methanogenic microbial consortium (Kayembe et al., 2013). Additionnally, the toxic effects of phenolic compounds on anaerobic degradation of glucose were found to be dependent on many parameters

such as the autoxidation level, the apolarity, as well as the type and number of substitutions of the phenolic compounds (Hernandez and Edyvean, 2008). Consistently with other by-products, the inhibitory level of the phenolic compounds was also linked to microbial ecosystem exposition to such compounds (Hierholtzer et al. 2013; Olguin-lora et al., 2003).

5.3.2. Effect of by-products combination on AD

As previously mentioned for hydrogen production, when by-products are present together, synergy effects may occur, reducing considerably the threshold value for inhibition compared if such by-products are added separately (Mussatto and Roberto, 2004; Bellido et al., 2011; Larsson et al., 1999). According to our knowledge, no study has reported until now the exact synergistic impact between phenolic compounds and furan derivatives on anaerobic digestion performances. Nonetheless, some authors already suggested a possible synergistic effect of simultaneous addition of furfural and 5-HMF on anaerobic digestion (Badshah et al., 2012b; Janzon et al., 2014). When they were added in combination at a concentration of 1 g L^{-1} each, they did not show a synergistic inhibitory effect but affected the kinetics by increasing the lag phase, corresponding probably to the time of adaptation of the microbial community. In contrast, by adding 2 g L^{-1} of furfural and 3 g L^{-1} of 5-HMF in combination, the methane produced was lower than that obtained by adding furfural and 5-HMF individually (Badshah et al., 2012b). To study the synergetic effect of by-products on AD and to compare the effect caused by the addition of the same compounds separately, the inoculums were sampled from the same AD plant but at different times of sampling. Therefore it is difficult to conclude whether this inhibition was due to synergistic impact of by-products or due to the different inoculum microbial diversity (Badshah et al., 2012b).

Badshah et al. (2012b) showed recently that addition of furfural and 5-HMF at concentrations generally found in hydrolyzates issued from thermal and thermo-chemical pretreatment of lignocellulosic substrates did not have any impact on anaerobic digestion of complex substrates such as cellulose. This suggests that neither hydrolysis nor methanogenesis step were inhibited in that case. By supplementing a solution of cellulose with two media containing both furfural and 5-HMF mixtures at concentrations higher than generally found in lignocellulosic hydrolyzates - Medium 1: furfural: 0.13 g L^{-1}; 5-HMF: 0.37 g L^{-1}; Medium

2: furfural: 0.80 g L^{-1}; 5-HMF: 0.46 g L^{-1} -, no increase in the lag phase nor reduction of the methane yield was observed. These results are in agreement with studies that did not found apparent inhibition of anaerobic digestion after dilute-acid pretreatment of lignocellulosic biomass, such as sunflower stalks, sugarcane bagasse, mewsprint wates and besides the presence of furfural and 5-HMF in the hydrolyzate (Monlau et al., 2012b, Badshah et al. 2012a,b, Fox and Noike, 2004). As suggested by Vivekanand et al. (2012), it is difficult to establish clearly the absence of effect of by-products on anaerobic digestion as the beneficial effect of opening the plant cell structure and liberating sources of nutrition during pretreatments can cover partially or totally the chemical inhibitory effect of the by-products. Consequently, supplementary works on using by-products added separately or in mixtures, at a cellular level, are still required to state definitely their exact effects and their possible synergistic effect.

5.3.3. Degradation of by-products and microbial adaptation

In several studies, the necessity of adapting the microbial inoculum was shown through the increase of lag-phase or decrease of digestion rates in presence of pretreatment by-products (Benjamin et al. 1984, Barakat et al., 2012; Fox and Noike, 2004). Fox and Noike (2004) reported a long lag phase of 10-15 days during anaerobic digestion of newspapers waste hydrolyzate containing phenolic and furanic compounds. Such observation suggested that an appropriate period of adaption of the microbial ecosystems is required to enhance the development of specific microbial populations fermenting organic molecules to methane in presence of by-products (Fox and Noike, 2004). Rosenkranz et al. (2013) investigated this adaptation period by sequential addition of phenol at 200 mg L^{-1} in a batch anaerobic digester and they observed a reduction of the lag phase. Indeed, the lag phase was reduced from 20-25 days to 4 days after the third addition, showing an adaptation of the microbial inoculum to phenolic compounds. Park et al. (2013) showed that 5-HMF at 3 g L^{-1} extended the lag phase of anaerobic digestion of acetate with an initial granular sludge concentration of 4.5 g VSS L^{-1}. Interestingly, an increase of the inoculum concentration up to 20 g VSS L^{-1} completely overcame the lag phase period, emphasizing that the by-products/inoculum concentration ratio plays an important role in the adaptation process. Consequently, adaptation of inoculum or increase in its initial concentration seem to be two promising methods to overcome long lag phase that can occur during anaerobic

digestion of hydrolyzates containing pretreatment by-products.

Contrarily to the dark fermentation process, anaerobic digestion seems more efficient to remove and degrade furan derivatives. Badshah et al. (2012a) reported that furfurals generated during dilute-acid pre-treatment of sugarcane bagasse did not cause any apparent inhibition of methane production and were even degraded during the anaerobic process. Similarly, Barakat et al. (2012) investigated the anaerobic degradation of furfurals and 5-HMF at 2 g L^{-1} as sole carbon sources and reported methane yields corresponding to 74% and 78% of the theoretical values. Rivard and Grohmann (1991) showed previously that in a CSTR (Continuous Stirred Tank Reactor) system where furfural was continuously added, 80% of the biogas theoretically expected was recovered. In this case, furfural was converted into several intermediates, including furfuryl alcohol, furoic acid and acetate, before its final conversion to methane and carbon dioxide (Rivard and Grohmann, 1991). In general, microorganisms appear to have the ability to convert both 5-HMF and furfural into less inhibitory compounds. Inhibitory effects are therefore gradually reduced as long as initial concentrations are not too high (i.e. from 0 to 2 g L^{-1}) (Boyer et al., 1992).

Additionally, removal and degradation of phenolic compounds during anaerobic digestion were previously reported in several studies (Barakat et al., 2012; Rosenkranz et al., 2013; Fox et al., 2003). Barakat et al. (2012) investigated the anaerobic degradation of vanillin and syringaldehyde at 2 g L^{-1} as sole carbon sources. Vanillin was found to be recalcitrant to microbial degradation with a measured methane potentials representing 17% of the theoretical value compared to 84% for syringaldehyde. Fox et al. (2003) investigated the effect of phenolic and heterocyclic compounds during semi-continuous anaerobic digestion of news-print wastes pre-treated by alkaline subcritical water method. They found that phenolic compounds at a concentration of 7 mg L^{-1} were totally and rapidly degraded, except for 4-methylcatechol which needed around 200 days of microbial adaptation prior to any degradation(Fox et al., 2003). Adaptation of the mixed inoculum is also an important parameter to be considered when dealing with the degradation of phenolic compounds (Olguin-lora et al., 2003; Rosenkranz et al., 2013; Fang et al., 2004). By using phenol-adapted anaerobic sewage sludge, Fang et al. (2004) reported phenol degradation up to 2 g L^{-1} in a UASB (upflow anaerobic sludge blanket) reactor. Similarly, by a progressive increase of phenol concentration leading to microbial ecosystem adaptation, high rates of phenol removal were observed during anaerobic digestion (Rosenkranz et al., 2013). However, at a microbiological level, the increase of phenol concentration for

inoculum adaptation was accompanied by a sharp decrease of microbial diversity and a progressive selection of the most adapted phylotypes (Rosenkranz et al., 2013). Main anaerobic microorganisms involved in degradation of phenolic compounds at mesophilic and thermophilic conditions were recently reviewed (Leven et al., 2012). Interestingly, Leven et al. (2012) concluded that the degradation efficiency of different phenols correlated well inversely with the process temperature. A higher degradation efficiency was observed at mesophilic than at thermophilic temperature (Leven et al., 2005; Leven et al., 2012). Possible explanation was likely related to slight differences in microbial diversity, particularly in the abundance of phenol-degrading bacteria among the ecosystem and/or the presence of temperature-sensitive enzymes (Leven et al., 2012).

Benzoate was found to be a key intermediate of phenol degradation during anaerobic digestion at ambient and mesophilic temperature (Fang et al., 2004; Hoyos-Hernandez et al., 2013). Based on DNA cloning analysis, Fang et al. (2004) identified different groups of microoganisms involved in phenol degradation : *Desulfotomaculum* sp. and *Clostridium* sp. were found to be responsible for the conversion of phenols into benzoate, which was further degraded by *Syntrophus* sp. into acetate and H_2/CO_2. Methanogens lastly converted acetate and H_2/CO_2 into methane (Fang et al., 2004). Later, Fang et al. (2006) suggested that phenol could be transformed via a caproate pathway instead of benzoate pathway under thermophilic conditions.

Finally, the efficiency of phenolic compound removal during anaerobic digestion plays also an important role prior to reuse the digestate as fertilizer to avoid any environmental disturbance (Leven et al., 2006). Indeed, phenolic compounds, besides to affect sometimes downstream microbial processes, are also harmful and can affect the quality of the digestate, if not removed. They act negatively on soil microorganisms such as ammonia oxidizing bacteria and further reduce the productivity and sustainability of cultivated soils. (Leven et al., 2012, Leven et al., 2006, Pell and Torstensson, 2002).

[Table 5. Summary of the main impact of by-products released during thermal and thermo-chemical pretreatments on anaerobic digestion using mixed cultures as inoculum]

6. Final remarks and future scope

In mixed microbial cultures, a thorough analysis of literature data showed that dark fermentation is more sensitive than anaerobic digestion to by-products generated during thermal and thermo-chemical pretreatments of lignocellulosic and algal biomass. Even though inhibition of methane production was observed in several cases, the minimal inhibitory concentration (MIC) of by-products for anaerobic digestion is far higher than the MIC for fermentative hydrogen production with 10 g/L against only 1.5-2 g/L for 5-HMF, respectively. Moreover, anaerobic digestion was found to be efficient to remove at moderate concentration most of the inhibitory by-products. These findings are surprising because the dark fermentation process corresponds to the first steps of the anaerobic digestion process. However, several differences between both processes can explain this observation: first, mixed-cultures used in dark fermentation are generally heat-treated and therefore are highly simplified and very specific for H_2 production. Comparatively, the anaerobic digestion inoculum has a better adaptability to environmental changes. Second, micro-organism concentrations are usually higher in methane potential tests (BMP) than in batch hydrogen production tests (BHP) since the ratio substrate/micro-organisms or by-product/micro-organisms is far higher in hydrogen tests, suggesting a higher and direct effect of by-products on the microbial growth. Moreover, a major impact of the presence of such pre-treatment by-products is the increase of lag-phase of biological processes. Microbial community adaptation is therefore recommended prior to inoculation. Although hydrogen production is strongly inhibited in presence of by-products, carbohydrates are nonetheless degraded during the process and converted into other metabolites such as propionate, ethanol or lactate. This metabolic shift is mainly due to microbial community changes from H_2 producers to H_2 consumers or competitors. These compounds can be further converted to methane and, therefore, the overall methane yields are not affected.

However, several bottlenecks remain to understand exactly the effect of such by-products on dark fermentation and anaerobic digestion processes. Some of the challenges that need to be addressed are listed below:

(1) More investigations have to been performed to determine exactly the Minimal Inhibitory Concentration (MIC) of each byproducts (furfural, 5-HMF…) on both dark fermentation and

anaerobic digestion processes.

(2) More investigations on the possible synergistic effect between the different by-products on the anaerobic fermentative processes represent also a challenging work for the future as information are clearly missing in the literature.

(3) Few studies have shown the degradation of by-products in continuous process. These results raise the questions of the impact of reactor mode (batch or continuous) and of inoculum adaptation

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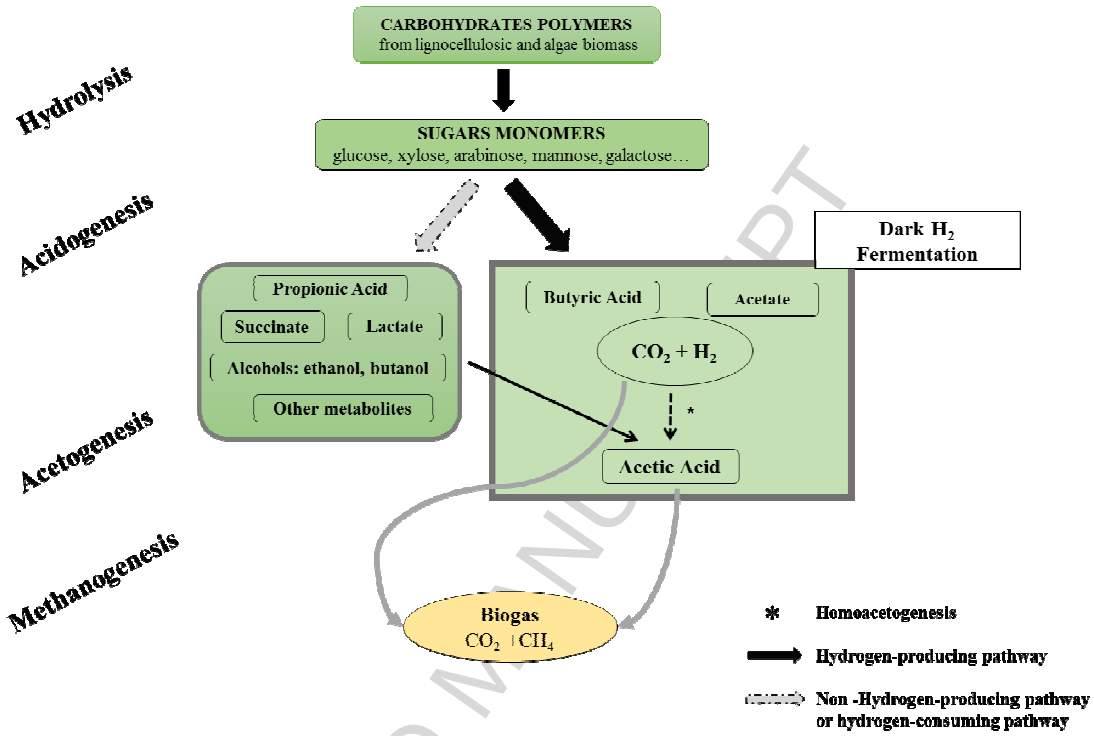

Fig. 1. Scheme of carbohydrate polymers degradation through dark fermentation and anaerobic digestion bioprocesses operated with mixed cultures (adapted from Monlau et al., 2013a).

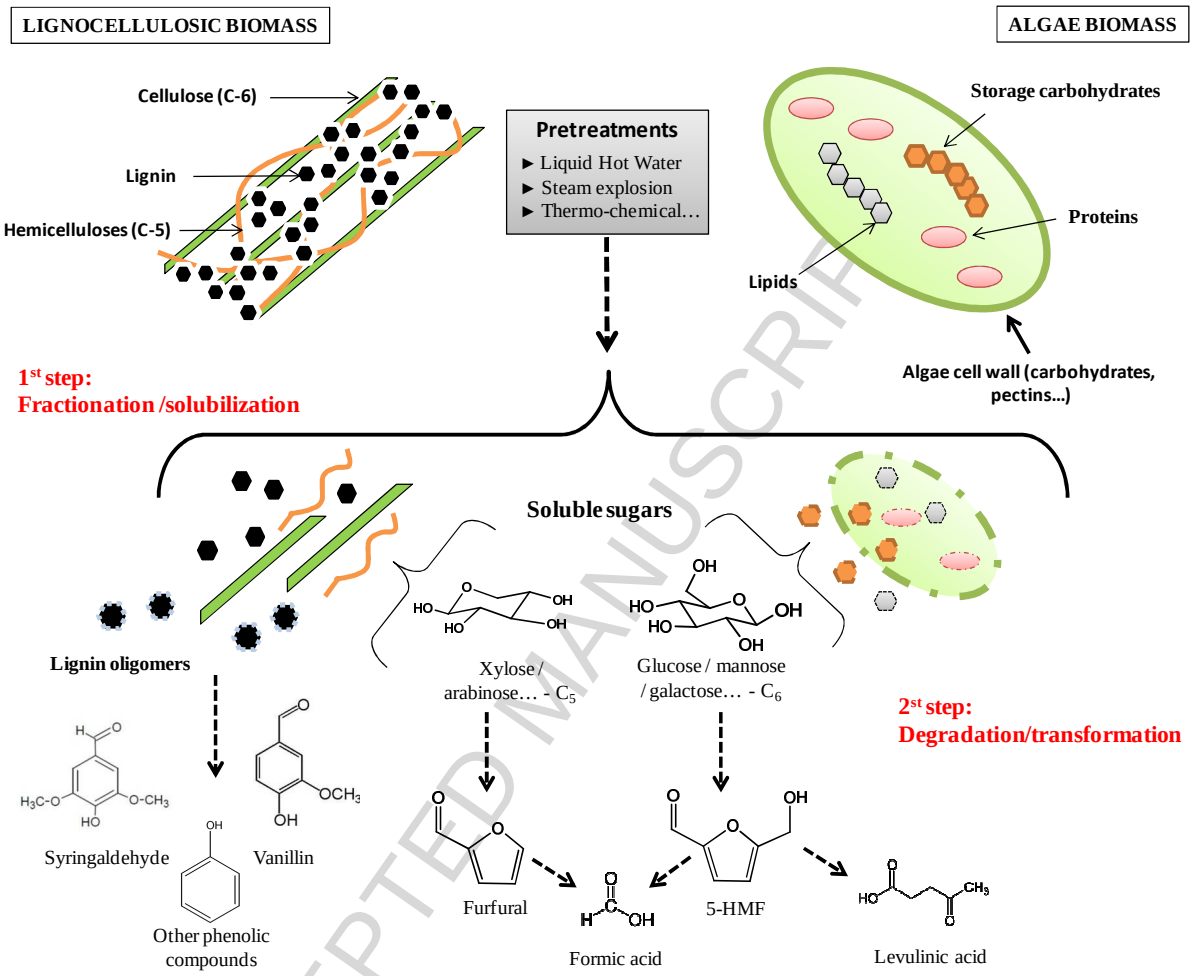

Fig. 2. Global scheme of by-products generation (i.e. aliphatic acids, furanic derivatives and phenolic compounds) after thermal and thermo-chemical pretreatments of lignocellulosic and algal biomass.

Table 1. Chemical composition (i.e. cellulose, hemicelluloses and lignin) of various lignocellulosic substrates expressed in terms of % DM (Dry Matter) (adapted and modified from Ruiz et al., 2013)

Substrates	Celluloses (%)	Hemicelluloses (%)	Lignin (%)	References
GRASS / GRAMINAE				
Wheat straw	33-40	20-34	13-18	(Talebnia et al., 2010 ; Ruiz et al., 2013)
Sunflower stalk	34-42	19-21	12-30	(Akpinar et al., 2009; Diaz et al., 2011; Monlau et al., 2012b; Ruiz et al., 2013)
Barley straw	36	12-29	8-15	(Sun et al., 2005; Persson et al., 2009; Park and Kim, 2012)
Rice straw	35-37	16-22	12-15	(Hsu et al., 2010; Yadav et al., 2011)
Maize stems	36-38	10-30	3.5-10.5	(Sun et al., 2005; Monlau et al., 2012a)
Corn Stover	37-39	23-31	14-18	(Lee, 1997; Sills and Gossett, 2012; Theerarattananoon et al., 2012; Saha et al., 2013)
Switch grass	17-36	20-28	18-26	(Gnansounou and Dauriat, 2010; Sills and Gossett, 2012)
Sweet sorghum	27-38	15-20	10-20	(Li et al., 2010; Monlau et al., 2012a)
Forage sorghum	32-36	20-23	18-26	(Li et al., 2010; Manzanares et al., 2012)
Miscantus	38-43	24-37	19-25	(Kurakake et al., 2001; Velasquez et al., 2003; Brosse et al, 2009)
Switchgrass	33-41.2	26-31	17-19	(Keshwani and Cheng, 2009 ; Hu et al., 2011)
SOFTWOOD				
Larix leptolepis	43	24	29	(Park and Kim, 2012)
Eucalyptus	34-44	18-19	19-30	(Romani et al., 2010; Gnansounou and Dauriat, 2010; Park and Kim 2012)
Softwood stems	40-50	25-35	25-35	(Sun and Cheng, 2002)
Pinus radiata	45	22.5	27	(Araque et al., 2008)
Spruce	44	21	29	(Shafiei et al., 2010)
CELLULOSE WASTE				
Newspapers	60.3	16.4	12.4	(Lee et al., 2010)
Paper sludges	60.8	14.2	8.4	(Peng and Chen, 2011)

Table 2. Chemical composition (i.e. lipids, proteins and carbohydrates) of various macro and micro algae expressed in terms of % DM.

Substrates	Lipids (%)	Proteins (%)	Carbohydrates (%)	References
MACROALGAE				
GREEN ALGAE				
Codium fragile	1.8	10.9	32.3	(Jung et al., 2011b)
Enteromorpha linza	1.8	31.6	37.4	(Jang et al., 2012)
Ulva Lactuca	6.2	20.6	54.3	(Kim et al., 2011)
RED ALGAE				
Gelidium amansii	0 - 3.1	15.6 - 16.3	61 - 67.3	(Park et al., 2011a; Jung et al., 2011b)
Porphyra tenera	4.4	38.7	35.9	(Jung et al., 2011b)
Gracilaria verrucosa	3.2	15.6	33.5	(Jung et al., 2011b)
BROWN ALGAE				
Laminaria Japonica	1.8 - 2.4	9.4 - 14.8	51.9 - 59.7	(Jung et al., 2011b; Kim et al., 2011)
Hizikia fusiforme	0.4 - 1.5	5.9 - 13.9	28.6 - 59	(Jung et al., 2011b; Jang et al., 2012)
Saccharina Japonica	0.5	19.9	44.5	(Jang et al., 2012)
Sargassum fulvellum	1.6	10.6	66	(Jang et al., 2012)
Ecklonia stolonifera	2.4	13.6	48.6	(Jung et al., 2011b)
Unduria pinnatifida	1.8 - 2.0	15.9 - 18.3	40.1 - 52	(Jung et al., 2011b; Jang et al., 2012)
Sargassum fulvelum	1.4	13	39.6	(Kim et al., 2011)
MICROALGAE				
Scenedesmus obliqus	12 - 14	50 - 56	10 - 17	(Becker, 1994)
Scenedesmus dimorphus	16 - 40	8 - 18	21 - 52	(Becker, 1994)
Chlorella vulgaris	14 - 22	51 - 58	12 - 17	(Becker, 1994)
Porphyridium cruentum	9 - 14	28 - 39	40 - 57	(Becker, 2006)
Spirogyra sp.	11 - 21	6 - 20	33 - 64	(Becker, 1994)
Prymnesium parvum	22 - 38	28 - 45	25 - 33	(Becker, 1994)
Porphyridium cruentum	9 - 14	28 - 39	40 - 57	(Becker, 1994)
Anabaena cylindrica	4 - 7	43 - 56	25 - 30	(Becker, 1994)
Spirulina Platensis	16	42	11	(Sydney et al., 2010)
Euglena gracilis	14 - 20	39 - 61	14 - 18	(Becker, 2007)
Dunaliela tertiolecta	11	29	13	(Sydney et al., 2010)
Dunaliela salina	6 - 9	12 - 57	32 - 55	(Feinberg, 1984; Becker, 2007)
Chlamydomonas	23	17	59	(Feinberg, 1984)
Cyclotella cryptica	18	13	67	(Feinberg, 1984)

Table 3. Composition of various hydrolyzates issued from algae and lignocellulosic biomass in terms of soluble carbohydrates and by-products generation

Pretreatments	Substrates	Pre-treatment conditions	Soluble sugars and by-products concentration (g L^{-1})								∑ soluble sugars/∑ furans[b]	∑ soluble sugars/∑ furans + phenols	References
			Hexose sugars	Pentose sugars	Soluble sugars[a]	Furfural	5-HMF	Phenols	Acetate	Formate			
Thermal	Corn stover	Hot water, 200°C, 10 min; biomass/liquid:1:20; log Ro = 3.94	3.7	8.8	12.5	1	0.2	-	5.3	-	10.4	-	(Bondesson et al., 2013)
	Eucalyptus	Hot water, 200°C, 20min, biomass/liquid: 1/10 w/v; log Ro = 4,24	2.33	8.36	10.69	3.29	0.44	-	2.21	-	2.9	-	(Wei et al., 2013b)
	Mapple chips	Hot water, 200°C, 20 min; 23 % (w/w TS); log Ro = 4.24	0.6	9.2	9.8	4.1		1.3	13.1		2.4	1.8	(Kim et al., 2011)
	Wheat straw	Steam explosion, 220°C, 2.5 min, biomass/liquid: 1:5; log Ro = 3.93	4.4	25	29.4	0.89	0.26	-	7.5	-	25.5	-	(Alvira et al., 2010)
	Wheat straw	Hot water, 80°C, 6min follow by 180°C, 15 min follow by 190°C, 3 min	2.9	12.6	15.5	0.25	0.14	0.14	-	-	39.7	29.2	(Kaparaju et al., 2009)
	Laminaria Japonica macroalga	Hot water, 170°C, 5 min; biomass/liquid:1:12; log Ro = 2.76	2.22	1.76	3.98	1.79	-	-	-	-	-	-	(Jung et al., 2011b)
	Laminaria Japonica macroalga	Hot water, 170°C, 30 min; biomass/liquid:1:12; log Ro = 3.53	3.39	2.55	5.94	3.88	-	-	-	-	-	-	(Jung et al., 2011b)
Thermo-acidic	Cassava residues	170°C, 30 min; 4% (w/w) H_2SO_4; biomass/liquid:1:10 (w/v)	5.1	9.4	14.5	2.05		-	5.1	-	7.1	-	Zhang et al., 2011
	Rice husk	121°C, 180 min, 4% v/v H_2SO_4, biomass/liquid:1:10 (w/v)	1.83	8.61	10.44	0.94		0.15	1.96	-	11.1	9.6	(Cao et al., 2009)
	Rice straw	160°C, 25 min; 1% H_2SO_4; biomass/liquid:1:10	5.95	11.7	17.65	2.5	0.3	-	1.9	-	6.3	-	(Hsu et al., 2010)

Pretreatments	Substrates	Pre-treatment conditions	Soluble sugars and by-products concentration (g L^{-1})								∑ soluble sugars/∑ furans[b]	∑ soluble sugars/∑ furans + phenols	References
			Hexose sugars	Pentose sugars	Soluble sugars[a]	Furfural	5-HMF	Phenols	Acetate	Formate			
	Rice straw	(w/v), CS = 2.5 160°C, 5 min; 1% H_2SO_4; biomass/liquid:1:10 (w/v), CS = 1.8	4.01	14.4	18.41	0.1	0.9	-	1.3	-	18.41	-	(Hsu et al., 2010)
	Saccharum biomass	Oxalic acid 3.21 % w/w, 158°C, 16 min, biomass/liquid 1:4 w/w, log Ro = 2.93	2.6	32.1	34.7	0.68	0.1	6.58	3.6	-	44.5	4.7	(Scordia et al., 2010)
	Saccharum biomass	Oxalic acid 3.21 % w/w, 182°C, 34 min, biomass/liquid 1:4 w/w, log Ro = 3.93	2.8	16.3	19.1	6.08	0.78	7.21	7.7	-	2.8	1.4	(Scordia et al., 2010)
	Spruce	150°C, 20 min, 2,4% w/w H_2SO_4, CS = 1.8	21.1	5.7	26.8	0.5	0.5		4.8	0.7	26.8	-	(Larsson et al., 1999)
	Spruce	240°C, 5 min, 2,4% w/w H_2SO_4, CS = 4.5	12.1	1.1	13.2	1.2	1.26		4.8	215	5.36	-	(Larsson et al., 1999)
	C. vulgaris algae	HCl, 3 % v/w, 60 min, biomass/liquid 1:10 w/w.	-	-	-	-	4.3	-	-	-	-	-	(Yun et al., 2013)
	Gelidium amansii macroalga	180°C, 15 min; 0.5% H_2SO_4 (w/w); biomass/liquid: 10 (w/v), CS = 2.7				13.32			1.33	0.33			(Park et al., 2013)
Thermo-alkaline	P. Juliflora stem	NaOH 0.1M, 30°C, 18h, biomass/liquid 1:10 w/v	-	-	3.16	0.135		3.94	-	-	23.4	0.8	(Naseeruddin et al., 2013)
	P. Juliflora stem	KOH 0.3M, 30°C, 18h, biomass/liquid 1:10 w/v	-	-	7.43	0.842		3.32	-	-	8.8	1.8	(Naseeruddin et al., 2013)
	P. Juliflora stem	Ammonia 3% w/v, 30°C, 18h, biomass/liquid 1:10 w/v	-	-	2.44	1.559		5.12	-	-	1.6	0.3	(Naseeruddin et al., 2013)
	Rice husk	Alkaline peroxide-soaking, 1% H_2O_2 w/v, 1.6% Overnight at 25°C	7.97	1.12	9.09	0.08	0.032	5.23	2.2	0.82	81.1	1.7	(Banerjee et al., 2011)

[a] Soluble sugars are the sum of hexose and pentose sugars
[b] Furanic compounds are the sum of furfural and 5-HMF

Table 4. Summary of the impact of by-products released during thermal and thermo-chemical pretreatments on dark fermentative biohydrogen production using mixed cultures as inoculum

Inoculum, fermentation process	Substrate	By-products concentrations in fermentative processes	Results	References
Heat pretreated sludge, batch, 37°C, pH=5.5, 50 days I conc. : 250 mg COD L^{-1}	None	furfural: 1 g L^{-1} 5-HMF: 1 g L^{-1} phenol : 1 g L^{-1} vanillin: 1 g L^{-1} syringaldehyde: 1 g L^{-1}	Y_{H2} =0 and no biogas production	(Quéméneur et al., 2012)
Heat pretreated sludge, batch, 37°C, pH=5.5, 50 days I conc. : 250 mg COD L^{-1}	Xylose: 5g L^{-1}	none	Y_{H2} =1.67 mol/$mol_{xylo\ cons}$ λ=3.2 d	
		furfural: 1 g L^{-1}	Y_{H2} =0.51 mol/$mol_{xyl\ cons}$ λ=19 d	
		5-HMF: 1 g L^{-1}	Y_{H2} =0.40 mol/$mol_{xyl\ cons}$ λ=10 d	
		phenol: 1 g L^{-1}	Y_{H2} =1.28 mol/$mol_{xyl\ cons}$ λ=23 d	
		vanillin: 1 g L^{-1}	Y_{H2} =1.30 mol/$mol_{xyl\ cons}$ λ=16.5 d	
		syrinhgaldehyde:1 g L^{-1}	Y_{H2} =1.39 mol/$mol_{xyl\ cons}$ λ=8.1 d	
Heat pretreated sludge, batch, 35°C, pH=5.5, I conc. : 8.8 to 9.45 g VS L^{-1}	Galactose :10g_{COD} L^{-1}	5-HMF: 0, 0.5, 1 g L^{-1}	Y_{H2} : 1.3-1.6 mol $_{H2}$/mol_{sugar} and 100% sugar utilisation	(Park et al., 2011a)
		5-HMF : 1.2 g L^{-1}	Y_{H2}: 0.6 mol $_{H2}$/mol_{sugar} and 100% sugar utilisation	
		5-HMF : 1.5 and 2 g L^{-1}	Y_{H2} =0 but 100% sugar utilisation	
	Gelidium amansii pretreated (H_2SO_4, 150°C) 24.5 gTS L^{-1}	5-HMF : 2.4 g L^{-1}	Y_{H2} =0 mol H_2 / mol sugars added	
		5-HMF:0.02 –0.05 g L^{-1}	Y_{H2} =0.9-1.07 mol H_2 / mol sugars added	
Mixed anaerobic granular sludge, batch, 37°C, pH =5.5, I conc.: 2 g VSS L^{-1}	Glucose: 5g L^{-1}	Furfural: 0.5 g L^{-1}, 5-HMF: 0.5 g L^{-1}, without linoleic acid pretreatment of inoculum	Y_{H2} from 0.67 to 1.46 mol H_2 / mol glucose	Veeravalli et al., 2013
		Furfural: 0.5 g L^{-1}, 5-HMF: 0.5 g L^{-1}, with linoleic acid pretreatment of inoculum	Y_{H2} from 1.5 to 1.7 mol H_2 / mol glucose	
		Furfural: 1 g L^{-1}, HMF: 1 g L^{-1}, with linoleic acid pretreatment of inoculum	Y_{H2} from 0.91 to 1.28 mol H_2 / mol glucose	
Heat pretreated sludge, batch, 37°C, pH=5.5, 27 days I conc. : 250 mg VS L^{-1}	Sunflower stalks, pretreated (HCl, 170°C)	furfural: 1.15 g L^{-1} 5-HMF: 0.13 g L^{-1} total phenols 0.02 g L^{-1}	Y_{H2} =0 within 10 days	(Monlau et al., 2013b)
	Glucose: 5 g L^{-1}	No addition	Y_{H2} =2.04 mol/mol $_{glc\ cons}$	
	Glucose: 5 g L^{-1} +3.75% sunflower stalks hydrolysate (dilute acid pre-treatment, 170°C, 1h, 4g HCl/100gTS)	furfural: 0.043 g L^{-1} 5-HMF: 0.005 g L^{-1} total phenols 0.001 g L^{-1}	Y_{H2} =1.89 mol/mol $_{glc\ cons}$	
	Glucose: 5 g L^{-1} +7.5% sunflower stalks hydrolysate	furfural: 0.086 g L^{-1} 5-HMF: 0.009 g L^{-1} total phenols 0.002 g L^{-1}	Y_{H2} =0.44 mol/mol $_{glc\ cons}$	
	Glucose: 5 g L^{-1} +15% sunflower stalks hydrolysate	furfural: 0.172 g L^{-1} 5-HMF: 0.019 g L^{-1} total phenols 0.003 g L^{-1}	Y_{H2} =0 metabolic shift towards ethanol 1.6 mol_{EtOH}/mol $_{glc\ cons}$	

Inoculum, fermentation process	Substrate	By-products concentrations in fermentative processes	Results	References
	Glucose: 5 g L^{-1} +35% sunflower stalks hydrolysate	furfural: 0.402 g L^{-1} 5-HMF: 0.044 g L^{-1} total phenols 0.007 g L^{-1}	Y_{H2} =0 metabolic shift towards ethanol 1.9 $mol_{EtOH}/mol_{glc\ cons}$	
Enriched hydrogenogenic culture from lab CSTR, adapted to hydrolysate Batch, 70°C	Wheat straw hydrolysate (hydrothermal pre-treatment) Sugars: 0.8-3.9 g L^{-1}	Sugars: 0.8 g L^{-1} Furfural: 0.013 g L^{-1} 5-HMF: 0.007 g L^{-1} total phenols: 0.007 g L^{-1}	Y_{H2} =318 $mL/g_{sugar\ added}$ λ=12 h Furfural remaining: 0.3 mg/L 5-HMF remaining: 0.0 mg/L	(Kongjan et al., 2010)
		Sugars: 3.1 g L^{-1} Furfural: 0.050 g L^{-1} 5-HMF: 0.028 g L^{-1} total phenols 0.028 g L^{-1}	Y_{H2} =187 $mL/g_{sugar\ added}$ λ=10 h Furfural remaining: 2 mg/L 5-HMF remaining: 0.6 mg/L	
		Sugars: 3.9 g L^{-1}Furfural: 0.056 g L^{-1} 5-HMF: 0.035 g L^{-1} total phenols 0.035 g L^{-1}	Y_{H2} =148 $mL/g_{sugar\ added}$ λ=39 h Furfural remaining: 7 mg/L 5-HMF remaining: 0.8 mg/L	
Enriched-adapted culture, CSTR 70°C, HRT=3 d		Furfural: 0.05 g L^{-1} 5-HMF: 0.028 g L^{-1}	Y_{H2} =178 $mL/g_{sugar\ added}$ Furfural and 5-HMF were undetectable in the CSTR outlet	
Heat pretreated sludg, batch, 35°C, pH=5.5, I conc. : 1.14 gVS L^{-1}	*Laminaria japonica* pretreated (HCl+thermal) 20 g COD L^{-1}	5-HMF: 2-8 g L^{-1} in pretreated sample, concentration not available in fermentative process	Inverse relationship between 5-HMF concentration and H_2 yield (from 150 mLH_2/gTS to almost 0)	(Jung et al., 2011b)
Heat pretreated sludge, batch, 35°C, pH=5.5, I conc. : 1.14 gVS L^{-1}	*Laminaria japonica* pretreated (thermal at 170°C, 5-40 min) 20 g COD L^{-1}	Furfural: 1.8-4.8 g L^{-1} in pretreated sample, concentration not available in fermentative process	Increased of hydrogen production from range time varying from 5min to 20min. From 20min to 40min, no hydrogen potentials increase and augmentation in the lag phase.	(Jung et al., 2011b)
Heat pretreated sludge, batch, 45°C, pH=6.5	Rice straw hydrolysate (various acids, 150°C)	Not measured Removed by lime and activated carbon	Y_{H2} =0 within 10 days Y_{H2} = 5 to 10 $mmol/g_{straw}$	(Chang et al., 2011b)
Heat pretreated anaerobic sludge 105°C, 2h, batch 35°C, pH 5.5	Steam exploded corn stover (200°C, 1 min)	Furfural: 0.129 g L^{-1} 5-HMF: 1.74 g L^{-1}, concentration not available in fermentative process	Y_{H2} = 0.74 mol H_2 per liter of hydrolyzate, λ=24h	(Datar et al., 2007)
Heat pretreated sludge, batch, 45°C, pH=6.5	Rice straw hydrolysate (various acids, 150°C)	Removed by activated charcoal treatment Furfural: 0.044 g L^{-1} 5-HMF: 0.558 g L^{-1}, concentration not available in fermentative process	Y_{H2} = 0.74 mol H_2 per liter of hydrolyzate, λ=12h	(Chang et al., 2011b)
Elephant dung, Batch, 55°C, pH=5.5	Xylose + arabinose: 5 g L^{-1}each Sugar cane bagasse pretreated (1% H_2SO_4, 121°C, 1 h) Sugars 10 g L^{-1}	none	Y_{H2} =2.49 $mol/mol_{sugar\ cons}$	(Fangkum and Reungsan, 2011)
		Furfural and acetate	Y_{H2} =1.48 $mol/mol_{sugar\ cons}$	
Heat pretreated sludge (90°C, 20 min), batch, 35°C, pH=7.4, I conc. : 1.65 gVS L^{-1}	Ultrasound pre-treatment on microalgae C. *vulgaris* (10000 to 100000 kJ / kg TS)	untreated samples	Y_{H2} =31.1 mL/g_{TS}	(Yun et al., 2013)
		5-HMF: 0.02 to 0.41 g L^{-1} in pretreated sample, concentration not available in fermentative process	Y_{H2} =31.9 to 37.9 mL/g_{TS}	

Inoculum, fermentation process	Substrate	By-products concentrations in fermentative processes	Results	References
Heat pretreated sludge (90°C, 20 min), batch, 35°C, pH=7.4, I conc. : 1.65 gVS L^{-1}	Acid pre-treatment (HCl) on microalgae C. *vulgaris*	untreated samples	Y_{H2} =31.1 mL/g_{TS}	
		5-HMF: 0.23 to 1.51 g L^{-1} in pretreated sample, concentration not available in fermentative process	Y_{H2} =29.3 to 35.7 mL/g_{TS}	
		5-HMF: 3.12 to 4.30 g L^{-1} in pretreated sample, concentration not available in fermentative process	Y_{H2} =25.3 to 13.6 mL/g_{TS}	
Heat pretreated sludge (90°C, 20 min), batch, 35°C, pH=7.4, I conc. : 1.65 gVS L^{-1}	Acid pre-treatment (HCl) + ultrasound on microalgae C. *vulgaris*	untreated samples	Y_{H2} =31.1 mL/g_{TS}	
		5-HMF: 0.15 to 2.95 g L^{-1} in pretreated sample, concentration not available in fermentative process	Y_{H2} =34.7 to 29.7 mL/g_{TS}	
		5-HMF: 3.40 g L^{-1} in pretreated sample, concentration not available in fermentative process	Y_{H2} =24.2 mL/g_{TS}	

Y_{H2} : hydrogen yield λ: lag-phase time I conc. : Inoculum concentration in anaerobic fermenter

Table 5. Summary of the main impact of by-products released during thermal and thermo-chemical pretreatments on anaerobic digestion using mixed cultures as inoculum

Inoculum, fermentation process	Substrates	By-product concentration in fermentation process	Results	References
Anaerobic sludge, batch, 37°C 50 d	Acetic and propionate	Phenol: 0 g L^{-1}	Control (Crt)	(Fedorak and Hrudey, 1984)
		Phenol: 0.50 g L^{-1}	higher CH_4 production than Crt	
		Phenol: 1.2 g L^{-1}	same CH_4 production as Crt	
		Phenol: 2 g L^{-1}	lower CH_4 production than Crt	
		Phenol: 3 g L^{-1}	CH_4 production near 0	
Anaerobic sludge, batch, 37°C, 140 d	Cellulose: 2.7 g L^{-1}	Phenol: 0 g/L	Control (Crt)	(Chapleur et al., 2013)
		Phenol: 0.01 to 0.05 g L^{-1}	same CH_4 production as Crt	
		Phenol: 0.5 to 1 g L^{-1}	same CH_4 production as Crt, but two phases of degradation	
		Phenol: 2 g L^{-1}	CH_4 production near 0	
		Phenol: 4 g L^{-1}	No CH_4 production	
Granular sludge, batch, 35°C, 35 d, I conc. : 4.5 gVSS L^{-1}	Acetate (AC) 3.0 gCOD L^{-1}	5-HMF : 0 g L^{-1}	Y_{CH4}=320 mL/gCOD-AC; 3 d*	(Park et al., 2011b)
		5-HMF : 1 g L^{-1}	Y_{CH4}=400 mL/gCOD-AC; 17d*	
		5-HMF : 2 g L^{-1}	Y_{CH4}=480 mL/gCOD-AC; 15 d*	
		5-HMF : 3 g L^{-1}	Y_{CH4}=550mL/gCOD-AC, 32 d*	
		5-HMF : 5 g L^{-1}	Y_{CH4}=710 mL/gCOD-AC, 30 d*	
		5-HMF : 10 g L^{-1}	Y_{CH4}=0 mL/gCOD-AC, 35 d*	
Granular sludge, batch, 35°C, 22 d, I conc. : 20 gVSS L^{-1}		5-HMF : 0 g L^{-1}	Y_{CH4}=320 mL/gCOD-AC; 8 d*	
		5-HMF : 1 g L^{-1}	Y_{CH4}=440 mL/gCOD-AC; 8 d*	
		5-HMF : 2 g L^{-1}	Y_{CH4}=470 mL/gCOD-AC; 18 d*	
		5-HMF : 3 g L^{-1}	Y_{CH4}=550mL/gCOD-AC, 20 d*	
		5-HMF : 5 g L^{-1}	Y_{CH4}=700 mL/gCOD-AC, 20 d*	
		5-HMF : 10 g L^{-1}	Y_{CH4}=0 mL/gCOD-AC, 22 d*	
Anaerobic inoculum from a digester of a wastewater treatment plant, batch, 37°C, 25d, I conc. : 6 g VS L^{-1}	Cellulose: 12g L^{-1}	None	Y_{CH4} =352 mL/g_{VS}	(Badshah et al., 2012b)
		Furfural: 1 g L^{-1}	Y_{CH4} =345 mL/g_{VS}	
		Furfural: 2 g L^{-1}	Y_{CH4} =384 mL/g_{VS}	
		Furfural: 4 g L^{-1}	Y_{CH4} =338 mL/g_{VS}	
		5-HMF: 1g L^{-1}	Y_{CH4} =324 mL/g_{VS}	
		5-HMF: 3g L^{-1}	Y_{CH4} =353 mL/g_{VS}	
		5-HMF: 6g L^{-1}	Y_{CH4} =0 mL/g_{VS}	
		Furfural/5-HMF: 1-1g L^{-1}	Y_{CH4} =357 mL/g_{VS}	
		Furfural/5-HMF: 2-3g L^{-1}	Y_{CH4} =17 mL/g_{VS}	
		Furfural/5-HMF: 4-6g L^{-1}	Y_{CH4} =0 mL/g_{VS}	
Granular sludge, batch, 37°C, 42 d, I conc. : 5 g VS L^{-1}	None	Furfural: 2 g L^{-1}	Y_{CH4} =430 mL/$g_{VS,}$ λ=4 d	(Barakat et al., 2012)
		5-HMF: 2 g L^{-1}	Y_{CH4} =450 mL/$g_{VS,}$ λ=14 d	
		vanillin : 2 g L^{-1}	Y_{CH4} =105 mL/$g_{VS,}$ λ=4 d	
		syringaldehyde: 2g L^{-1}	Y_{CH4} =453 mL/$g_{VS,}$ λ=4 d	
Granular sludge, batch, 37°C, 20 d, I conc. : 5 g VS L^{-1}	Xylose: 1 g L^{-1}	None	Y_{CH4} =300 mL/$g_{VS,}$ λ=0 d	
		Furfural: 1 g L^{-1}	Y_{CH4} 300 mL/$g_{VS,}$ λ=1 d	
		5-HMF: 1 g L^{-1}	Y_{CH4} =345 mL/$g_{VS,}$ λ=1 d	
		vanillin : 1 g L^{-1}	Y_{CH4} =225 mL/$g_{VS,}$ λ=0 d	
		syringaldehyde: 1g L^{-1}	Y_{CH4} =400 mL/$g_{VS,}$ λ=0 d	
Predigested active sludge, batch, 35°C, 250 d, I conc.: 1.3 gVSS L^{-1}	None	Phenol 100 mg L^{-1}	B = 21.7%, , λ=17 d, 38*	(Hernandez and Edyvean, 2008)
		Phenol 200 mg L^{-1}	B =27.3 %, , λ=24 d, 45*	
		Phenol 400 mg L^{-1}	B = 32.2 %, , λ=31 d, 103*	
		Phenol 800 mg L^{-1}	B =1.1 %, , complete inhibition of the digestion process	
		Phenol 1600 mg L^{-1}	B = 1.7 %, complete inhibition of the digestion process	
Rumen, batch	Filter paper cellulose 4 g L^{-1}	vanilic acid: 6 to 30mM	No methane inhibition compared to Crt	(Op den Camp et al.,1988)
		ferulic acid: 5 to 25mM	No methane inhibition compared to Crt	
		p-coumaric acid: 6 to 3o mM	Total methane inhibition at 30 mM	
Municipal sewage sludge, batch, 35°C, 21 d, I conc. : 4 g VS L^{-1}	Avicel cellulose: 2 g L^{-1}	None	Y_{CH4} =730 mLbiogas/$g_{VS,}$	(Janzon et al., 2014)
		Medium 1: Furfural: 5 mg L^{-1} 5-HMF: 30 mg L^{-1}	Y_{CH4} =705 mLbiogas/ $g_{VS,}$	

Inoculum, fermentation process	Substrates	By-product concentration in fermentation process	Results	References
		Medium 2: Furfural: 5 mg L^{-1} 5-HMF: 60 mg L^{-1}	Y_{CH4} =670 mLbiogas/ $g_{VS,}$	
Anaerobic inoculum from a digester of a wastewater treatment plant, batch, 37°C, 25d, I conc. : 6 g VS L^{-1}	Cellulose: 12g L^{-1}	None	Y_{CH4} =348 mL/g_{VS}	(Badshah et al., 2012b)
		Medium 1: Furfural: 0.13 g L^{-1} 5-HMF: 0.37 g L^{-1}	Y_{CH4} =359 mL/g_{VS}	
		Medium 2: Furfural: 0.80 g L^{-1} 5-HMF: 0.46 g L^{-1}	Y_{CH4} =369 mL/g_{VS}	
Anaerobic inoculum from biogas plant treating pig manure and food wastes, batch, 37°C, 18 d, I conc. : 6 g VS L^{-1}	Sugarcane bagasse hydrolyzate (2g H_2SO_4 /100gTS, 121°C, 15 min)	Furfural: 0.13 g L^{-1} 5-HMF: not detected	Y_{CH4} = 173 mL/g_{VS} (higher than raw sugarcane bagasse) Furfural was not detected at the end of anaerobic digestion process	(Badshah et al., 2012a)
Granular sludge, bach, 37°C, 35 d, I conc. : 5 gVS L^{-1}	Sunflower stalks pretreated (4g HCl /100 gTS, 170°C,1h), 35 gTS L^{-1}	Furfural: 1.35 g L^{-1} 5-HMF: 0.13 g L^{-1}	Y_{CH4} = 233 mL/g_{VS} (21% higher than raw sunflower stalks)	(Monlau et al. 2012b)
Anaerobic sludge from a wastewater treatment plant, batch, 35°C, 60 d	Wet oxidation of newspaper wastes at different temperatures	Furans:0.005 to 0.065 g L^{-1}	No impact on methane production but lag phase of 10-15 days	(Fox and Noike, 2004)
		Phenols:0.441 to 0.552 g L^{-1}	Removal of lignin derivatives between 84% to 100% and furans removals varied between 87% and 96%.	

* Approximate time needed to reach methane production plateau, λ: lag-phase time, I conc.: Inoculum concentration in anaerobic fermenters, B: Anaerobic biodegradability.

Highlights

Dark fermentation is more sensitive than anaerobic digestion to furanic and phenolic compounds

By-products strongly inhibit hydrogen production by dark fermentation

At moderate concentration, most of by-products are removed by anaerobic digestion

In dark fermentation process, by-products lead to a metabolite shift from acetate, butyrate and H_2 to lactate, ethanol and propionate