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A simple overview of toxicity of ionic liquids and designs of biocompatible ionic liquids

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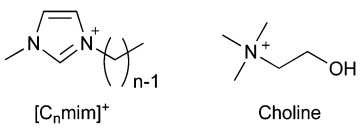
Evaluation of toxicity of ionic liquids has been less prioritized, compared to the development of new ionic liquids and their applications. Focus on the toxicity of ionic liquids should be enhanced, since ionic liquids have been intensively industrialized for decades. Their toxicity is related to not only biological applications but also others, since accidents, such as leakage, can occur at any time. This current review aims at systematically summarizing the general trend between the chemical structure and toxicity of ionic liquids across biological species. It also provides a perspective on the current strategies for the development of low-toxicity ionic liquids and their applications.

1 Introduction

The field of ionic liquids[1–6] began with the discovery of ethyl ammonium nitrate in 1914 by Paul Walden.[7] It has grown extensively after the groundbreaking report titled "air and water stable ionic liquids" by Wilkes and Zaworotko.[8,9] Ionic liquids have been applied and industrialized in various fields, such as batteries,[2,10] adsorbents,[11,12] biomass conversion,[13–15] lubricants,[16] stationary and mobile phases of chromatography,[17–21] catalysts,[22–26] CO_2 capture,[27] and pharmaceutical/biomedical applications[28–30] to date.[31] Their toxicity, however, is a concern in all applications, besides their biological applications. For example, in an industrial application, safety concerns arise if humans come in contact with them during the process. Further concerns include problems where ionic residues remain in the final product or leak into the environment. Overall, irrespective of the application, it is difficult to completely ignore the toxicity of ionic liquids.

In the soil, near a landfill in Newcastle, England, $[C_8mim]^+$ cations (structure shown in Fig. 1) have been found and reported to be of concern to human health.[32,33] The origin of this ionic liquid-like cation is unknown, and no health hazard has been reported to date. However, since ionic liquids are beginning to be used in a wide variety of practical applications, it is imperative to understand their toxicity better. This current review is aimed at discussing the toxicity of ionic liquids and ways to avoid the same.

As is quite obvious, "ionic liquid toxicology" is a relatively new field, and many aspects of it are yet to be understood. In addition, the toxicity values vary widely across species, and comparison of each value is difficult. Although there are several advanced reviews[34–40] that describe the toxicities in specific species, one-by-one, they are too high level for new entrants and students to comprehend and there is no paper yet providing a simple overview of the general and fundamental toxicological principles across species, except for a review[41] published at the primitive stage of this field (2007), to the best of the author's knowledge. The current review is aimed at systematically



$[C_nmim]^+$ Choline

Fig. 1 Cationic structures of ionic liquids relevant to this review.

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Kosuke Kuroda

Dr Kosuke Kuroda received his PhD from the Graduate School of Engineering, Tokyo University of Agriculture and Technology in 2014. He then moved to the Graduate School of Natural Science and Technology, Kanazawa University, where he was a research assistant professor. Dr Kuroda established his independent career as an assistant professor in 2017 and as an associate professor in 2020 at the same place. The primary focus of his research is to develop novel ionic liquids, with low toxicity and other functions, such as cellulose dissolution ability.

summarizing the toxicology of ionic liquids as simply as possible, as a mini-review. This would also help the readers to access appropriate references in order to understand the individual toxicity aspects.

2 Toxicity of ionic liquids

2-1. Overview of ionic liquid toxicity

The toxicity of ionic liquids has been studied using a wide range of targets, from proteins to animals. For proteins, acetylcholinesterase, an enzyme related to nerve signaling, is frequently used as a model.[34,35] Many reports have been published on other proteins as well.[2,34,35,42–48] This current review is focused on living organisms, in particular, cells, which are the smallest units of living organisms, and higher organisms. First, the toxicity of $[C_8mim]^+$-based ionic liquids (mentioned in the introduction) is reviewed. EC_{50}, a commonly used indicator of toxicity, is defined as the concentration of ionic liquids at which the growth of cells and microorganisms is halved compared to that without the ionic liquid. In other words, the higher the EC_{50}, the lower the toxicity. For example, the EC_{50} value of $[C_8mim]Cl$ for rat leukemia IPC-81 cells is 0.102 mmol L^{-1} (23 mg L^{-1}, $\approx$0.002 wt%).[49] This indicates that the addition of only 1 or 2 earpicks of $[C_8mim]Cl$ in a 1 liter PET bottle would inhibit cell growth. Since the EC_{50} of methanol is 1584 mmol L^{-1} (51000 mg L^{-1}, $\approx$5 wt%),[49] $[C_8mim]Cl$ may be considered highly toxic. In fact, many publications have reported the concept of using ionic liquids as sterilizers or anticancer agents.[50–52]

However, not all ionic liquids are as toxic as $[C_8mim]Cl$; each type of ionic liquid has a different toxicity. The factor most relevant to the toxicity of ionic liquids is the alkyl chain length of the cations. The longer the alkyl chain length of the cation, the more toxic the ionic liquids are. Although there are many classifications of organisms, almost all organisms, including microorganisms,[53] animal cells,[49] plants,[54] crustaceans,[55] fish,[56] and mammals,[57] are affected by the toxicity, as the alkyl chain length of the cation increases. The relationship between the alkyl chain length of ionic liquids and the EC_{50} against IPC-81 cells is shown in Fig. 2. The EC_{50} value can be seen to decrease almost exponentially with the elongation of the alkyl chain from 2 to 10 carbons. For the short-chain $[C_2mim]Cl$, the EC_{50} value is 7.2 mmol L^{-1} (1100 mg L^{-1}, $\approx$0.1 wt%), an order of magnitude higher than that of $[C_8mim]Cl$. However, the value is still much smaller than that of methanol, indicating its high toxicity. Therefore, shortening of the alkyl chain length of the cation is not sufficient to reduce toxicity. In other words, the commonly used ionic liquids are basically highly toxic.

When the alkyl chain of the cation is approximately shorter than the butyl group, the cation head and the anion can also affect the toxicity.[34] However, the relationship between these structures and toxicity is speculated to be due to complex interrelated factors, and a systematic theory is yet to be developed.

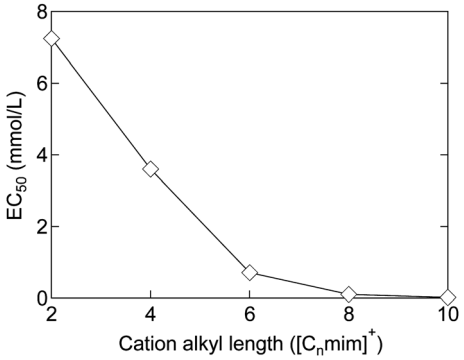


Fig. 2 Relationship between the alkyl chain length and EC_{50} of $[C_nmim]Cl$ against IPC-81 cells.[58,59]

2-2. Toxicity to mammals

Toxicity to mammals (mice and rats) is briefly reviewed, which should be most concerned when used in applications. The dose of $[C_4mim]Cl$ at which 50% of rats die (LD_{50}) is reported to be approximately 550 mg kg^{-1}.[60] LD_{50} of methanol and dimethyl sulfoxide (DMSO; a low toxicity organic solvent) is 5600 and 15 000–30 000 mg kg^{-1}, respectively,[61,62] indicating $[C_4mim]Cl$ to be highly toxic. As an adverse effect besides death, weight gain was observed. The alkyl chain length also has a significant effect on toxicity in mammals.[57] The toxicity of $[C_2mim]Cl$ was hardly apparent even after multiple doses of 2000 mg kg^{-1} day^{-1} in mice. On the other hand, $[C_{10}mim]Cl$ caused death or fetal teratogenicity even at 100 mg kg^{-1} day^{-1}.

In case of dermal, rather than oral administration, toxicity varies depending on the solvent mixed with the ionic liquid.[60,63] When ionic liquids were administered using water as the solvent, LD_{50} for rats was $>$2000 mg kg^{-1} for both males and females. In contrast, when dimethylformamide was used as the solvent, LD_{50} for female rats was 800–2000 mg kg^{-1} (for males, $>$2000 mg kg^{-1}). Other adverse effects include inflammation, decreased activity, red liquid discharge from the eyes, and intestinal discoloration.

When administered orally or transdermally, the majority of the ionic liquids were absorbed into the bloodstream and ultimately excreted relatively quickly from the body as feces and urine.[63] This absorption and efflux are believed to be related to organic cation transporters. On the other hand, the absorption and efflux behaviors are reported to be less dependent on cationic species.[64,65]

The carcinogenicity of ionic liquids has also been investigated *in vitro*.[66] The Ames test, which detects the changes in DNA sequences, suggested that at least some bromide-based ionic liquids are not carcinogenic. However, there are some ionic liquids that show values close to the standard value for a positive result (namely carcinogenic), and further studies would be required in that aspect.

2-3. Mechanism of toxicity

As has been explained above, the longer the alkyl chain of a cation, the higher the toxicity. The mechanism has been described in the literature as follows: the alkyl chains of cations are inserted into the cell membrane, making it impossible to maintain the cell membrane (Fig. 3).[67–70] The alkyl chains of cations are inserted *via* the following steps: (1) a positively

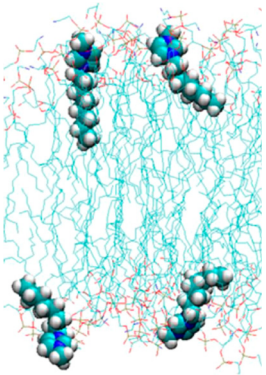


Fig. 3 Cell membrane and the inserted $[C_8mim]^+$ cation. Adapted with permission from the literature.[67] Copyright 2014 American Chemical Society.

charged cation comes in close contact with a negatively charged phosphate group of the cell membrane; (2) the alkyl chain of the cation interacts with the acyl group (long-chain alkyl group) of the cell membrane *via* hydrophobic interaction and gets inserted into the cell membrane.

To understand the mechanism underlying the toxicity of ionic liquids, the cation of $[C_2mim]Cl$ has been suggested to enter the cell *via* a transporter and affect mitochondria;[71,72] it alters the membrane potential of mitochondria, ultimately causing apoptosis (cell death).

3 Designs of low-toxicity ionic liquids

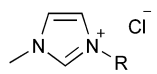
3-1. Introduction of polar groups

Increasing the polarity of alkyl chains of cations can suppress their hydrophobic interactions to cell membrane molecules. For example, introduction of a hydroxy group at the end of alkyl chain improves the EC_{50} by an order of magnitude or more (Table 1).[73,74] The polar group does not necessarily have to be at the end of the alkyl chain; introduction of an oxygen atom in the middle of the alkyl chain can also reduce EC_{50} greatly.[73] However, it should be noted that the EC_{50} value may not decrease depending on the position of the oxygen atom.

3-2. Bio-derived ionic liquids

Ionic liquids composed of bio-derived ions (sometimes called bionic liquids) are expected to be less toxic. Bio-derived cations are not many in number, and therefore, choline cations are often used. Choline exists as a metabolite of the neurotransmitter, acetylcholine, and as a polar head group of cell membrane molecules (*e.g.*, phosphatidylcholine). Choline cations are at least considerably less toxic than $[C_4mim]^+$ cations.[75,76] Chloride, acetate, citrate, and amino acid-derived anions have been reported as anions.[77,78] Among them, choline ionic liquids with chloride, acetate, glutamate, and aspartate anions have low toxicity, with the minimum growth inhibitory concentration against *E. coli* being 500–750 mM or higher (*e.g.*, the case of choline chloride: >100 g L^{-1}).[76] However, bio-derived ions are not necessarily less toxic; for example, choline tryptophanate is relatively toxic (the minimum growth inhibition concentration being 23 mM, ≈ 7 g L^{-1}). However, it is still less toxic than typical ionic liquids, such as $[C_4mim]BF_4$ (the minimum growth inhibition concentration being 2 mM).

Table 1 Effect of cationic side chains (–R) on EC_{50} against IPC-81 cells.[58,59,73]

–R for 	EC_{50} (mmol L^{-1})
Ethyl	7.2
Butyl	3.6
3-Hydroxypropyl	>20
Ethoxymethyl	4.0
2-Methoxyethyl	>20

3-3. Zwitterionization

Artificial ionic liquids are not necessarily toxic. Introducing an anionic moiety, the most polar functional group, at the end of a cationic alkyl chain, *i.e.*, zwitterionization,[79] can result in very low toxicity.[44,80–84] While the approach would be the same as in Section 3-1, the effect would be highly powerful. For example, the EC_{50} of carboxylate-type zwitterions against *E. coli* is much higher than that of choline acetate (Table 2).[80–82] While choline acetate shows no strong effect on *E. coli* growth (EC_{50}), it is highly toxic to fermentation (Fig. 4 and Table 2). On the other hand, zwitterions do not show strong toxicity toward either growth or fermentation. This might be caused by the high concentration of acetate, which is known as an inhibitor. The compatibility to fermentation enables applying ionic liquids to various biological conversions such as bioethanol production from cellulosic biomass (see the next section). The results, therefore, indicate that zwitterions have one of the lowest toxicities among the various ionic liquids.

4. Applications of low-toxicity ionic liquids: bioethanol production

Various applications of low-toxicity ionic liquids are currently being considered, like other ionic liquids; some are bio-related applications and some are not, and Gomes *et al.* summarized them broadly.[29] Bioethanol production from cellulosic biomass

Table 2 EC_{50} of zwitterions and other solvents against *E. coli* KO11 and relative ethanol concentration in 0.5 mol L^{-1} zwitterions and choline acetate.[80,82]

	EC_{50} (g L^{-1})	Relative ethanol concentration (%)
OE_2imC_3C	158	96
C_1imC_3C	141	100
C_1imC_3S	>200	104
Choline acetate	70	15
DMSO	91	—
Ethanol	17	—
—(Control)	—	100

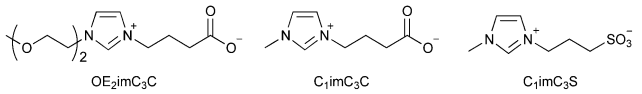


Fig. 4 Structures of zwitterions relevant to this review.

with ionic liquids is another recent development and is briefly reviewed here.

Production of bioethanol involves three steps, namely (1) pretreatment of biomass by ionic liquids, (2) enzymatic or acidic hydrolysis of polysaccharides, and (3) fermentation of glucose by microorganisms, such as yeasts. Although bioethanol can be obtained *via* three independent steps, it critically increases energy cost and results in negative energy balance. In particular, washing out ionic liquids with a large excess of water/alcohol costs energy. Therefore, successive or simultaneous processes would be required that only low-toxic ionic liquids can realize.

Besides low toxicity, pretreatment ability is an essential characteristic for ionic liquids to convert biomass. Therefore, carboxylate-type ionic liquids are often used for the purpose. The most typical cellulose-dissolving ionic liquid is toxic [C_2mim]OAc. Therefore, bio-derived choline acetate has been reported as a low-toxic solvent for biomass pretreatment.[80,85] The pretreatment ability of choline acetate is somewhat lower than that of [C_2mim]OAc, but it surely pretreats biomass.[86–88] The toxic effect of choline acetate on fermentation has been reported in the literature although it is less toxic to growth of microorganisms.[80] Choline-type ionic liquids with amino acid anions have been applied to bioethanol production.[86,89,90] In particular, research groups at The Joint BioEnergy Institute and related laboratories have been researching enthusiastically for industrialization.[13,14] They mainly use choline lysinate and have realized the conversion of tens of kilograms of woody biomass into ethanol.[13]

Imidazolium/carboxylate-type zwitterions (see Fig. 4) are also promising candidates for efficient bioethanol production.[80–82,91,92] Their low toxicity is remarkable, and fermentation can occur in an aqueous solution containing more than 50 wt% of the zwitterion.[80] The zwitterions can dissolve cellulose like [C_2mim]OAc, which is another advantage in biomass pretreatment. Imidazolium cations play a key role in dissolving cellulose.[93,94] Zwitterionization does not compromise any functions of ionic liquids, but it does lower toxicity—this is the most attractive feature of zwitterionization.

5. Conclusion

The term ''green solvent,'' which is a synonym for ionic liquids, is often confused with ''non-toxic''. However, we have outlined in this perspective that ionic liquids are not necessarily non-toxic, rather, depending on their structure, they may be more toxic than organic solvents. We have described, in this review, how to avoid such toxicity. Since ionic liquids are currently in the process of finding many applications, they may come in contact with the human body or might leak into the environment during various processes. If their toxicity is ignored, the end result could lead to environmental destruction and health hazards.

This field, toxicology of ionic liquids, has reached an inflection point because most commercial ionic liquids and synthesizable ionic liquids have already been evaluated. New designs of ionic liquids, based on their toxicity mechanisms, are necessary to develop low-toxicity ionic liquids in future. Development of artificial ionic liquids with low toxicity has been proven through precisely design considering effective mechanisms. In addition, the artificial ionic liquids can be freely modified and therefore easily functionalized, *e.g.*, biomass pretreatment ability. However, the problematic issue in this field is that only few researchers possess the required biological and chemical insight/techniques. Hopefully many researchers will enter this interdisciplinary field; collaborating, preferably, would be a more efficient and synergistic approach.

Conflicts of interest

There are no conflicts to declare.

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Notes and references

1 T. Welton, *Chem. Rev.*, 1999, **99**, 2071–2083.
2 M. Armand, F. Endres, D. R. MacFarlane, H. Ohno and B. Scrosati, *Nat. Mater.*, 2009, **8**, 621–629.
3 R. D. Rogers and K. R. Seddon, *Science*, 2003, **302**, 792–793.
4 Z. Lei, B. Chen, Y. M. Koo and D. R. MacFarlane, *Chem. Rev.*, 2017, **117**, 6633–6635.
5 B. D. Rabideau, K. N. West and J. H. Davis, *Chem. Commun.*, 2018, **54**, 5019–5031.
6 A. Brandt, J. Gräsvik, J. P. Hallett and T. Welton, *Green Chem.*, 2013, **15**, 550–583.
7 P. Walden, *Bull. Acad. Imp. Sci. St.-Petersbourg*, 1914, **8**, 405–422.
8 J. S. Wilkes and M. J. Zaworotko, *J. Chem. Soc., Chem. Commun.*, 1992, 965–967.
9 J. S. Wilkes, *Green Chem.*, 2002, **4**, 73–80.
10 M. Watanabe, M. L. Thomas, S. Zhang, K. Ueno, T. Yasuda and K. Dokko, *Chem. Rev.*, 2017, **117**, 7190–7239.

11 H. B. Salah, P. Nancarrow and A. Al-Othman, *Fuel*, 2021, **302**, 121195.
12 M. Yu, S. Zeng, Y. Nie, X. Zhang and S. Zhang, *Curr. Opin. Green Sustainable Chem.*, 2021, **27**, 100405.
13 C. A. Barcelos, A. M. Oka, J. Yan, L. Das, E. C. Achinivu, H. Magurudeniya, J. Dong, S. Akdemir, N. R. Baral, C. Yan, C. D. Scown, D. Tanjore, N. Sun, B. A. Simmons, J. Gladden and E. Sundstrom, *ACS Sustainable Chem. Eng.*, 2021, **9**, 4042–4053.
14 L. Das, E. C. Achinivu, C. A. Barcelos, E. Sundstrom, B. Amer, E. E. K. Baidoo, B. A. Simmons, N. Sun and J. M. Gladden, *ACS Sustainable Chem. Eng.*, 2021, **9**, 4422–4432.
15 H. Wang, G. Gurau and R. D. Rogers, *Chem. Soc. Rev.*, 2012, **41**, 1519–1537.
16 A. Somers, P. Howlett, D. MacFarlane and M. Forsyth, *Lubricants*, 2013, **1**, 3–21.
17 H. Nan and J. L. Anderson, *Trends Anal. Chem.*, 2018, **105**, 367–379.
18 Y. Fukaya, A. Tsukamoto, K. Kuroda and H. Ohno, *Chem. Commun.*, 2011, **47**, 1994–1996.
19 K. Kuroda, Y. Fukaya, T. Yamada and H. Ohno, *Anal. Methods*, 2015, **7**, 1719–1726.
20 M. D. Joshi and J. L. Anderson, *RSC Adv.*, 2012, **2**, 5470–5484.
21 M. Talebi, R. Patil and D. W. Armstrong, in *Commercial Applications of Ionic Liquids*, ed. M. B. Shiflett, Springer Nature; Switzerland, 2022, pp. 131–165.
22 A. C. Cole, J. L. Jensen, I. Ntai, K. L. T. Tran, K. J. Weaver, D. C. Forbes and J. H. Davis, *J. Am. Chem. Soc.*, 2002, **124**, 5962–5963.
23 K. Kuroda, K. Miyamura, H. Satria, K. Takada, K. Ninomiya and K. Takahashi, *ACS Sustainable Chem. Eng.*, 2016, **4**, 3352–3356.
24 H. Satria, K. Kuroda, T. Endo, K. Takada, K. Ninomiya and K. Takahashi, *ACS Sustainable Chem. Eng.*, 2017, **5**, 708–713.
25 R. Kakuchi, M. Yamaguchi, T. Endo, Y. Shibata, K. Ninomiya, T. Ikai, K. Maeda and K. Takahashi, *RSC Adv.*, 2015, **5**, 72071–72074.
26 S. Suzuki, Y. Shibata, D. Hirose, T. Endo, K. Ninomiya, R. Kakuchi and K. Takahashi, *RSC Adv.*, 2018, **8**, 21768–21776.
27 M. Ramdin, T. W. de Loos and T. J. H. Vlugt, *Ind. Eng. Chem. Res.*, 2012, **51**, 8149–8177.
28 W. Zhuang, K. Hachem, D. Bokov, M. J. Ansari and A. T. Nakhjiri, *J. Mol. Liq.*, 2022, **349**, 118145.
29 J. M. Gomes, S. S. Silva and R. L. Reis, *Chem. Soc. Rev.*, 2019, **48**, 4317–4335.
30 N. Adawiyah, M. Moniruzzaman, S. Hawatulaila and M. Goto, *MedChemComm*, 2016, **7**, 1881–1897.
31 N. V. Plechkova and K. R. Seddon, *Chem. Soc. Rev.*, 2008, **37**, 123–150.
32 P. M. Probert, A. C. Leitch, M. P. Dunn, S. K. Meyer, J. M. Palmer, T. M. Abdelghany, A. F. Lakey, M. P. Cooke, H. Talbot, C. Wills, W. McFarlane, L. I. Blake, A. K. Rosenmai, A. Oskarsson, R. Figueiredo, C. Wilson, G. E. Kass, D. E. Jones, P. G. Blain and M. C. Wright, *J. Hepatol.*, 2018, **69**, 1123–1135.
33 A. C. Leitch, T. M. Abdelghany, P. M. Probert, M. P. Dunn, S. K. Meyer, J. M. Palmer, M. P. Cooke, L. I. Blake, K. Morse, A. K. Rosenmai, A. Oskarsson, L. Bates, R. S. Figueiredo, I. Ibrahim, C. Wilson, N. F. Abdelkader, D. E. Jones, P. G. Blain and M. C. Wright, *Food Chem. Toxicol.*, 2020, **136**, 111069.
34 K. S. Egorova and V. P. Ananikov, *ChemSusChem*, 2014, **7**, 336–360.
35 C. W. Cho, T. P. T. Pham, Y. Zhao, S. Stolte and Y. S. Yun, *Sci. Total Environ.*, 2021, **786**, 147309.
36 J. Ranke, S. Stolte, R. Störmann, J. Arning and B. Jastorff, *Chem. Rev.*, 2007, **107**, 2183–2206.
37 T. P. Pham, C. W. Cho and Y. S. Yun, *Water Res.*, 2010, **44**, 352–372.
38 A. R. P. Gonçalves, X. Paredes, A. F. Cristino, F. J. V. Santos and C. Queirós, *Int. J. Mol. Sci.*, 2021, **22**, 5612.
39 J. Flieger and M. Flieger, *Int. J. Mol. Sci.*, 2020, **21**, 4253.
40 B. Kudłak, K. Owczarek and J. Namieśnik, *Environ. Sci. Pollut. Res. Int.*, 2015, **22**, 11975–11992.
41 D. Zhao, Y. Liao and Z. Zhang, *Clean: Soil, Air, Water*, 2007, **35**, 42–48.
42 T. Itoh, *Chem. Rev.*, 2017, **117**, 10567–10607.
43 K. Fujita, Y. Nikawa and H. Ohno, *Chem. Commun.*, 2013, **49**, 3257–3259.
44 K. Kuroda, C. Kodo, K. Ninomiya and K. Takahashi, *Aust. J. Chem.*, 2019, **72**, 139–143.
45 K. Fujita, D. R. MacFarlane, M. Forsyth, M. Yoshizawa-Fujita, K. Murata, N. Nakamura and H. Ohno, *Biomacromolecules*, 2007, **8**, 2080–2086.
46 S. K. Shukla and J. P. Mikkola, *Front. Chem.*, 2020, **8**, 598662.
47 L. Bui-Le, C. J. Clarke, A. Bröhl, A. P. S. Brogan, J. A. J. Arpino, K. M. Polizzi and J. P. Hallett, *Commun. Chem.*, 2020, **3**, 55.
48 T. Hirata, T. Takekiyo, Y. Yoshimura, Y. Tokoro, T. Ishizaki, Y. Kizuka and K. Kuroda, *RSC Adv.*, 2022, **12**, 11628–11631.
49 J. Ranke, K. Mölter, F. Stock, U. Bottin-Weber, J. Poczobutt, J. Hoffmann, B. Ondruschka, J. Filser and B. Jastorff, *Ecotoxicol. Environ. Saf.*, 2004, **58**, 396–404.
50 J. Gravel and A. R. Schmitzer, *Org. Biomol. Chem.*, 2017, **15**, 1051–1071.
51 A. R. Dias, J. Costa-Rodrigues, M. H. Fernandes, R. Ferraz and C. Prudêncio, *ChemMedChem*, 2017, **12**, 11–18.
52 J. Pernak, K. Sobaszkiewicz and I. Mirska, *Green Chem.*, 2003, **5**, 52–56.
53 S. M. Lee, W. J. Chang, A. R. Choi and Y. M. Koo, *Korean J. Chem. Eng.*, 2005, **22**, 687–690.
54 B. Jastorff, K. Mölter, P. Behrend, U. Bottin-Weber, J. Filser, A. Heimers, B. Ondruschka, J. Ranke, M. Schaefer, H. Schröder, A. Stark, P. Stepnowski, F. Stock, R. Störmann, S. Stolte, U. Welz-Biermann, S. Ziegert and J. Thöming, *Green Chem.*, 2005, **7**, 362–372.
55 M. Yu, S.-H. Wang, Y.-R. Luo, Y.-W. Han, X.-Y. Li, B.-J. Zhang and J.-J. Wang, *Ecotoxicol. Environ. Saf.*, 2009, **72**, 1798–1804.
56 N. F. M. Hafez, M. I. A. Mutalib, M. A. B. Bustam, M. El-Harbawi and J.-M. Leveque, *Procedia Eng.*, 2016, **148**, 830–838.
57 M. M. Bailey, P. L. Jernigan, M. B. Henson, J. Sturdivant, J. F. Rasco, A. N. Lovich, J. E. Lockhard, W. L. Hough, K. R. Di Bona, J. Beaird, J. Sherrill, R. P. Swatloski, R. D. Rogers and R. D. Hood, *Birth Defects Res., Part B*, 2010, **89**, 233–238.

58 J. Ranke, A. Müller, U. Bottin-Weber, F. Stock, S. Stolte, J. Arning, R. Störmann and B. Jastorff, *Ecotoxicol. Environ. Saf.*, 2007, **67**, 430–438.
59 M. H. Fatemi and P. Izadiyan, *Chemosphere*, 2011, **84**, 553–563.
60 T. D. Landry, K. Brooks, D. Poche and M. Woolhiser, *Bull. Environ. Contam. Toxicol.*, 2005, **74**, 559–565.
61 S. W. Jacob and E. E. Rosenbaum, *Headache: J. Head Face Pain*, 1966, **6**, 127–136.
62 Safety Data Sheet, Methanol, Tokyo Chemical Industry Co., Ltd. Revision Number 2, downloaded on Dec 27, 2021.
63 I. G. Sipes, G. A. Knudsen and R. K. Kuester, *Drug Metab. Dispos.*, 2008, **36**, 284–293.
64 Y. Cheng, S. H. Wright, M. J. Hooth and I. G. Sipes, *Drug Metab. Dispos.*, 2009, **37**, 909–916.
65 G. A. Knudsen, Y. Cheng, R. K. Kuester, M. J. Hooth and I. G. Sipes, *Drug Metab. Dispos.*, 2009, **37**, 2171–2177.
66 K. M. Docherty, S. Z. Hebbeler and C. F. Kulpa Jr., *Green Chem.*, 2006, **8**, 560–567.
67 G. S. Lim, J. Zidar, D. W. Cheong, S. Jaenicke and M. Klähn, *J. Phys. Chem. B*, 2014, **118**, 10444–10459.
68 R. J. Bingham and P. Ballone, *J. Phys. Chem. B*, 2012, **116**, 11205–11216.
69 B. Jing, N. Lan, J. Qiu and Y. Zhu, *J. Phys. Chem. B*, 2016, **120**, 2781–2789.
70 C. M. N. Mendonça, D. T. Balogh, S. C. Barbosa, T. E. Sintra, S. P. M. Ventura, L. F. G. Martins, P. Morgado, E. J. M. Filipe, J. A. P. Coutinho, O. N. Oliveira Jr. and A. Barros-Timmons, *Phys. Chem. Chem. Phys.*, 2018, **20**, 29764–29777.
71 Q. Dickinson, S. Bottoms, L. Hinchman, S. McIlwain, S. Li, C. L. Myers, C. Boone, J. J. Coon, A. Hebert, T. K. Sato, R. Landick and J. S. Piotrowski, *Microb. Cell Fact.*, 2016, **17**, 5.
72 S. Wu, L. Zeng, C. Wang, Y. Yang, W. Zhou, F. Li and Z. Tan, *J. Hazard. Mater.*, 2018, **348**, 1–9.
73 S. Stolte, J. r Arning, U. Bottin-Weber, A. Müller, W.-R. Pitner, U. Welz-Biermann, B. Jastorff and J. Ranke, *Green Chem.*, 2007, **9**, 760–767.
74 B. Jastorff, K. Mölter, P. Behrend, U. Bottin-Weber, J. Filser, A. Heimers, B. Ondruschka, J. Ranke, M. Schaefer, H. Schröder, A. Stark, P. Stepnowski, F. Stock, R. Störmann, S. Stolte, U. Welz-Biermann, S. Ziegert and J. Thöming, *Green Chem.*, 2005, **7**, 362–372.
75 W. Gouveia, T. F. Jorge, S. Martins, M. Meireles, M. Carolino, C. Cruz, T. V. Almeida and M. E. Araujo, *Chemosphere*, 2014, **104**, 51–56.
76 X. D. Hou, Q. P. Liu, T. J. Smith, N. Li and M. H. Zong, *PLoS One*, 2013, **8**, e59145.
77 Y. Fukaya, Y. Iizuka, K. Sekikawa and H. Ohno, *Green Chem.*, 2007, **9**, 1155–1157.
78 S. Hu, T. Jiang, Z. Zhang, A. Zhu, B. Han, J. Song, Y. Xie and W. Li, *Tetrahedron Lett.*, 2007, **48**, 5613–5617.
79 M. Yoshizawa, M. Hirao, K. Ito-Akita and H. Ohno, *J. Mater. Chem.*, 2001, **11**, 1057–1062.
80 K. Kuroda, H. Satria, K. Miyamura, Y. Tsuge, K. Ninomiya and K. Takahashi, *J. Am. Chem. Soc.*, 2017, **139**, 16052–16055.
81 H. Satria, K. Kuroda, Y. Tsuge, K. Ninomiya and K. Takahashi, *New J. Chem.*, 2018, **42**, 13225–13228.
82 T. Komori, H. Satria, K. Miyamura, A. Ito, M. Kamiya, A. Sumino, T. Onishi, K. Ninomiya, K. Takahashi, J. L. Anderson, T. Uto and K. Kuroda, *ACS Sustainable Chem. Eng.*, 2021, **9**, 11825–11836.
83 K. Kuroda, Y. Kohno and H. Ohno, *Chem. Lett.*, 2017, **46**, 870–872.
84 F. Jesus, H. Passos, A. M. Ferreira, K. Kuroda, J. L. Pereira, F. J. M. Gonçalves, J. A. P. Coutinho and S. P. M. Ventura, *Green Chem.*, 2021, **23**, 3683–3692.
85 K. Ninomiya, C. Ogino, M. Ishizaki, M. Yasuda, N. Shimizu and K. Takahashi, *Biochem. Eng. J.*, 2015, **103**, 198–204.
86 N. Sun, R. Parthasarathi, A. M. Socha, J. Shi, S. Zhang, V. Stavila, K. L. Sale, B. A. Simmons and S. Singh, *Green Chem.*, 2014, **16**, 2546–2557.
87 K. Ninomiya, T. Yamauchi, M. Kobayashi, C. Ogino, N. Shimizu and K. Takahashi, *Biochem. Eng. J.*, 2013, **71**, 25–29.
88 K. Ninomiya, H. Soda, C. Ogino, K. Takahashi and N. Shimizu, *Bioresour. Technol.*, 2013, **128**, 188–192.
89 X. D. Hou, T. J. Smith, N. Li and M. H. Zong, *Biotechnol. Bioeng.*, 2012, **109**, 2484–2493.
90 Q. P. Liu, X. D. Hou, N. Li and M. H. Zong, *Green Chem.*, 2012, **14**, 304–307.
91 A. Hachisu, H. Tobe, K. Ninomiya, K. Takahashi and K. Kuroda, *ACS Sustainable Chem. Eng.*, 2022, **10**, 6919–6924.
92 R. Kadokawa, T. Endo, Y. Yasaka, K. Ninomiya, K. Takahashi and K. Kuroda, *ACS Sustainable Chem. Eng.*, 2021, **9**, 8686–8691.
93 B. D. Rabideau, A. Agarwal and A. E. Ismail, *J. Phys. Chem. B*, 2013, **117**, 3469–3479.
94 T. Uto, K. Yamamoto and J. I. Kadokawa, *J. Phys. Chem. B*, 2018, **122**, 258–266.