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1 **Identification of disinfection by-product precursors by natural organic matter**
2 **fractionation: A critical review – invited article**

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17 membrane fractionation, chlorination

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38 Abstract

39 The presence of natural organic matter in water resources induces the formation of potentially
40 harmful disinfection by-products during drinking water disinfection. However, the identification of
41 disinfection by-product precursors from the complex natural organic matter mixture is very
42 challenging. Therefore, many studies focused on the fractionation of natural organic matter with
43 membranes or resins to better understand how and which organic matter fractions react during
44 chlorination. The outcomes of these studies are rather variable, therefore, a meta-analysis was
45 performed to compare the reactivity of the different fractions towards (un)regulated disinfection by-
46 products. In this study, we review for the first time the influence of key parameters such as
47 chlorination time and dose, specific ultraviolet absorbance ($SUVA_{254} = \text{UV absorbance at 254 nm}$
48 $\text{divided by the organic matter concentration}$) and the column capacity factor used during resin
49 fractionation by collecting results from almost 400 water samples from more than 80 different
50 publications. The major outcomes were: 1) hydrophobic compounds have 10-20 % higher reactivity
51 to both trihalomethane and haloacetic acid formation compared to hydrophilic compounds in waters
52 with high $SUVA_{254}$ ($>2 \text{ L}/(\text{mg}\cdot\text{m})$), while hydrophobic and hydrophilic compounds have equal
53 reactivity in waters with low $SUVA_{254}$. On the other hand, hydrophilic compounds are 20-80 % more
54 reactive towards emerging disinfection by-products, regardless of $SUVA_{254}$; 2) chlorination time and
55 dose seem to not change the reactivity ratio between the different fractions; 3) an increase in
56 column capacity factor can shift this ratio from hydrophobic to hydrophilic fractions and 4) dead-end,
57 stirred cell ultrafiltration membrane fractionation might not always produce sharply separated
58 fractions, which is mainly due to fouling. Therefore, no clear correlation could be found between
59 membrane fractions and all investigated disinfection by-product groups.

60 1 Introduction

61 Natural organic matter, ubiquitous in sources of drinking water, negatively affects drinking water
62 quality. It can contribute to an undesired taste, odor or color of the drinking water and to the
63 formation of biofilms and (pathogenic) bacterial regrowth by acting as nutrients in the distribution
64 system. Chlorine is the most commonly used disinfectant to inactivate waterborne pathogens and to
65 maintain a disinfectant residual in the distribution network. However, chlorine reacts with natural
66 organic matter to form various disinfection by-products and exposure to these by-products has been
67 associated with health issues such as bladder cancer (Diana et al., 2019). More than 700 disinfection
68 by-products have already been identified, where mainly four trihalomethanes and five haloacetic
69 acids are regulated in different countries (Richardson et al., 2007). The USA has set maximum
70 contaminant limits of trihalomethanes and haloacetic acids in drinking water to 80 and 60 µg/L
71 respectively, while trihalomethane levels in the EU cannot exceed 100 µg/L. Haloacetic acid
72 concentrations were recently limited in the EU to 60 µg/L (Council of the European Union, 2020; EPA,
73 2010).

74 Unregulated disinfection by-products such as haloacetonitriles, haloacetamides or haloketones are
75 formed in lower concentrations (typically low µg/L to ng/L) (Richardson et al., 2007). Nevertheless,
76 the toxicity of these compounds is higher than that of the regulated by-products and thus, these
77 compounds may cause greater public health issues. The presence of bromide and/or iodide in the
78 water matrix leads to the formation of brominated and iodinated disinfection by-products (Criquet
79 and Allard, 2021). These compounds are even more genotoxic and cytotoxic than their chlorinated
80 analogues, *e.g.* iodoacetic acid, which is the most genotoxic compound identified to date (Dong et
81 al., 2019; Wagner and Plewa, 2017).

82 In the past decades, many research focused on identifying natural organic matter compounds
83 responsible for disinfection by-product formation. However, dissolved organic carbon, *i.e.* the
84 fraction that passes through a 0.45 µm filter, is a very complex mixture of aromatic and aliphatic
85 hydrocarbons. The concentration, composition and chemistry are highly variable and depend on the
86 natural organic matter source, the season, temperature, pH and ionic strength of the water (Filella,
87 2009; Leenheer and Croue, 2003). Therefore, dissolved organic carbon is characterized by bulk
88 parameters such as total organic carbon and specific ultraviolet absorbance at 254 nm (SUVA₂₅₄) or
89 by more in-depth characterization techniques such as nuclear magnetic resonance spectroscopy,
90 Fourier transform infrared spectroscopy and 3D-fluorescence excitation-emission matrices (Filella,
91 2009; Matilainen et al., 2011).

92 This characterization is however very difficult due to the simultaneous presence of hundreds of
93 different molecules. Therefore, with fractionation processes, organic matter is split beforehand into

94 several fractions with similar physical or chemical properties. This can be done analytically by the use
95 of chromatographic methods such as high performance-size exclusion chromatography or field flow
96 fractionation, which both split the organic matter by size and shape (Matilainen et al., 2011; Pan et
97 al., 2016). Huber et al. (2011) developed a method that consists of liquid chromatography coupled to
98 both an organic carbon detector and organic nitrogen detector. This technique is capable of
99 identifying five different fractions of organic matter; (a) biopolymers, (b) humic substances, (c)
100 building blocks, (d) low molecular weight acids and (e) low molecular weight neutrals.

101 With analytical fractionation, the different fractions are lost after analysis, because they are not
102 readily available as separate extracts nor in adequate volumes to conduct further experiments.
103 Therefore, preparative fractionation such as membrane or resin fractionation is performed to split
104 natural organic matter into available fractions or extracts with similar physical (with membranes) or
105 chemical (with resins) properties in sufficient quantities (Matilainen et al., 2011; Ratpukdi et al.,
106 2009). Subsequently, researchers seek to correlate these properties to certain water-related issues,
107 such as disinfection by-product formation, bacterial regrowth or membrane fouling behavior which
108 might be overly expressed with a certain fraction. Finally, precise solution strategies can be
109 developed targeting this specific fraction (Krzeminski et al., 2019; Pi et al., 2021; Sambo et al., 2020;
110 Yin et al., 2019).

111 Membrane and resin fractionation are widely used in an attempt to identify disinfection by-product
112 precursors. In this respect, fractionation parameters such as membrane and resin type, or
113 chlorination parameters such as chlorination dose, reaction time, pH and temperature are key
114 factors for the outcome and the interpretation of the results. Although research already looked into
115 the influence of chlorination parameters on bulk samples (Hua and Reckhow, 2008; Iriarte et al.,
116 2003), no assessments are done so far on how individual fractions react on certain changes in
117 chlorination parameters.

118 Therefore, this review will focus for the first time on (i) all the different membrane and resin
119 fractionation approaches used in the identification of disinfection by-product precursors and assess
120 their advantages and drawbacks and, (ii) critically evaluate if certain fractionation and chlorination
121 parameters can influence the formation of both regulated and unregulated disinfection by-products
122 in these fractions and identify their precursors.

123 2 Factors controlling fractionation and disinfection by-product 124 formation

125 Many research has been executed in the past to identify the most important precursors for
126 disinfection by-product formation. However, several approaches were used in these attempts. It is

127 therefore important to identify the parameters that are varied among the different papers, because
128 this can possibly affect the results and outcome. In this review, papers will be separated based on
129 their method and the influence of different parameters will be assessed to make a clear, statistical
130 comparison regarding disinfection by-product formation.

131 For membrane fractionation, both the membrane material and the pressure can influence the
132 filtration. Overall, regenerated cellulose is used and the pressure varies between 0.2 and 3.5 bar,
133 which is believed not to change the fractionation significantly (section 3.1). Furthermore, it appeared
134 that for resin fractionation, not the resin type, but the column capacity factor (k') is the only
135 parameter that differs largely between papers, having a value of 50 or 100 (Leenheer, 1981; Malcolm
136 and Maccarthy, 1992). Kitis et al. (2002) showed a gradual increase in trihalomethane and haloacetic
137 acid formation in a particular fraction when changing the column capacity factor from around 30 to
138 105 (section 4.1 for further discussion).

139 Chlorine is the principal disinfectant used in drinking water, an extensively studied reactant for
140 disinfection by-product formation potential and therefore, the only disinfectant reviewed here.
141 Temperature, pH, reaction time and chlorine dose are the 4 main parameters controlling disinfection
142 by-product formation kinetics (Hua and Reckhow, 2008). Ambient temperature and neutral pH are
143 reported in all papers collected and will therefore be assumed constant (sections 3 and 4). On the
144 other hand, the reaction time and chlorine dose is very variable among papers. Short reaction times
145 are mostly accompanied with low free chlorine residual (~ 1 mg Cl_2/L), while during long exposure,
146 chlorine is added in excess to seek reaction completion ($\sim 3 - 5$ mg Cl_2/L chlorine residual), as followed
147 by different APHA standard methods for the examination of water and wastewater such as 5710B
148 (sections 3 and 4). While the uniform formation condition test with short reaction time and low
149 chlorine dose illustrates distribution system conditions, the formation potential test determines a
150 maximal amount of disinfection by-products that could be formed through the complete reaction of
151 the disinfection by-product precursors with chlorine in a sample (Kanan and Karanfil, 2020).

152 Finally, specific ultraviolet absorbance (SUVA_{254}) is one of the most frequently used parameters to
153 characterize natural organic matter in a water source. SUVA_{254} is defined as the absorbance of UV at
154 254 nm divided by the organic matter concentration (Ho et al., 2013). This wavelength is especially
155 absorbed by aromatic species (Matilainen et al., 2011). In this review, the threshold between high
156 and low SUVA_{254} waters is set at 2 L/(mg·m). Since resin fractionation is mainly based on
157 hydrophobicity, this parameter might have an important role and will be included together with the
158 chlorination time, dose and column capacity factor when assessing the reactivity of different
159 fractions towards disinfection by-product formation.

160 3 Membrane fractionation

161 3.1 Principle of membrane fractionation

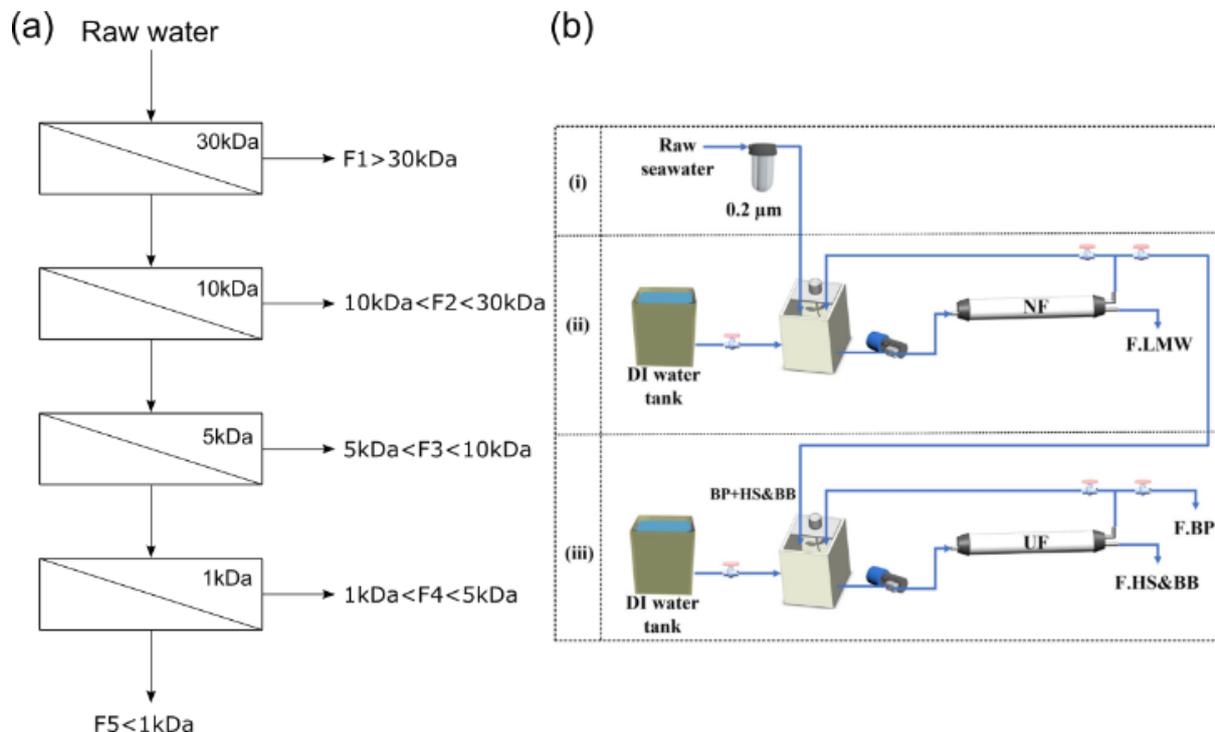
162 Generally, a series of ultrafiltration membranes with decreasing molecular weight cut-offs are used
163 to prepare fractions with different size-ranges (Fig. 1a). Regenerated cellulose membranes in dead-
164 end stirred cell configuration is the most frequently applied method. The molecular weight cut-off of
165 the membranes range from 0.5 kDa up to 100 kDa or even 500 kDa (Chang et al., 2001; Goslan et al.,
166 2004; Hu et al., 2015; Hua and Reckhow, 2007b; Hua et al., 2015; Özdemr, 2014; Wei et al., 2008b;
167 Xu et al., 2007; Zhang et al., 2020b; Zhao et al., 2009).

168 Generated membrane fractions are defined as a molecular weight range which is based on the
169 molecular weight cut-off of the membranes used, *e.g.* molecules that pass a membrane with a
170 molecular weight cut-off of 100 kDa, but are rejected by a membrane with one of 30 kDa are defined
171 as the 30-100 kDa fraction. This will be further called the theoretical molecular weight range of a
172 fraction. However, Goslan et al. (2004) and Zhao et al. (2009) characterized their generated
173 membrane fractions with size exclusion chromatography coupled to a ultraviolet detector at 254 nm.
174 From this, it was concluded that the chromatograms of all fractions from the respective paper are
175 largely overlapping. Furthermore, Zhao et al. (2009) reported that the apparent mean molecular
176 weight values of the fractions measured from the chromatography were lower than expected from
177 the molecular weight cut-offs.

178 This observation was also confirmed by other analytical techniques such as flow-field flow
179 fractionation (Assemi et al., 2004). Here, the minimum, maximum and mean molecular weight value
180 from each membrane fraction was determined. Fig. 2 shows the difference between the theoretical
181 molecular weight range (crossed pattern bars) and the real molecular weight range of a fraction
182 measured with flow-field flow fractionation (solid bars). Apart from the prominent overlap between
183 the fractions, it can be seen that the 10-30 kDa and > 30 kDa fraction only contain molecules which
184 are much smaller than 10 kDa, meaning that molecules bigger than 10 kDa were not present in the
185 raw water. However, it is contra-intuitive that molecules smaller than 10 kDa were retained by the
186 30 kDa membrane. For ultrafiltration membrane fractionation, most authors use a dead-end stirred
187 cell configuration. Here, the water flow is perpendicular to the membrane resulting in accumulation
188 of the retained compounds and thereby inducing fouling onto the membrane. This fouling layer will
189 act as an extra barrier, possibly retaining molecules smaller than the molecular weight cut-off of the
190 membrane. Furthermore, the pore sizes of membranes are known not to be uniform, but to have a
191 pore size distribution (Mulder, 1991). Therefore, molecular weight cut-off is defined as the molecular
192 weight of compounds that are retained by the membrane for only 90 %, which might explain the
193 partial overlap between the fractions (Chow et al., 2005; Zhao et al., 2009).

194 An alternative approach to perform a membrane fractionation was recently developed by Yin et al.
195 (2019) (Fig. 1b). With the use of both a nanofiltration and ultrafiltration membrane in spiral wound
196 modules, three distinct fractions from seawater were successfully obtained and characterized by
197 liquid chromatography, namely (i) a fraction containing 95 % biopolymers, (ii) a fraction with 93%
198 humic substances and their building blocks and (iii) a 87 % low molecular weight compound fraction
199 (Yin et al., 2019). After pretreating a raw water sample with a 0.2 µm filter to remove the particulate
200 matter, nanofiltration was performed to collect the low molecular weight molecules in the permeate
201 stream. Humic substances and biopolymers are rejected by the nanofiltration membrane and are fed
202 to a subsequent ultrafiltration membrane in which humic substances and biopolymers are separated

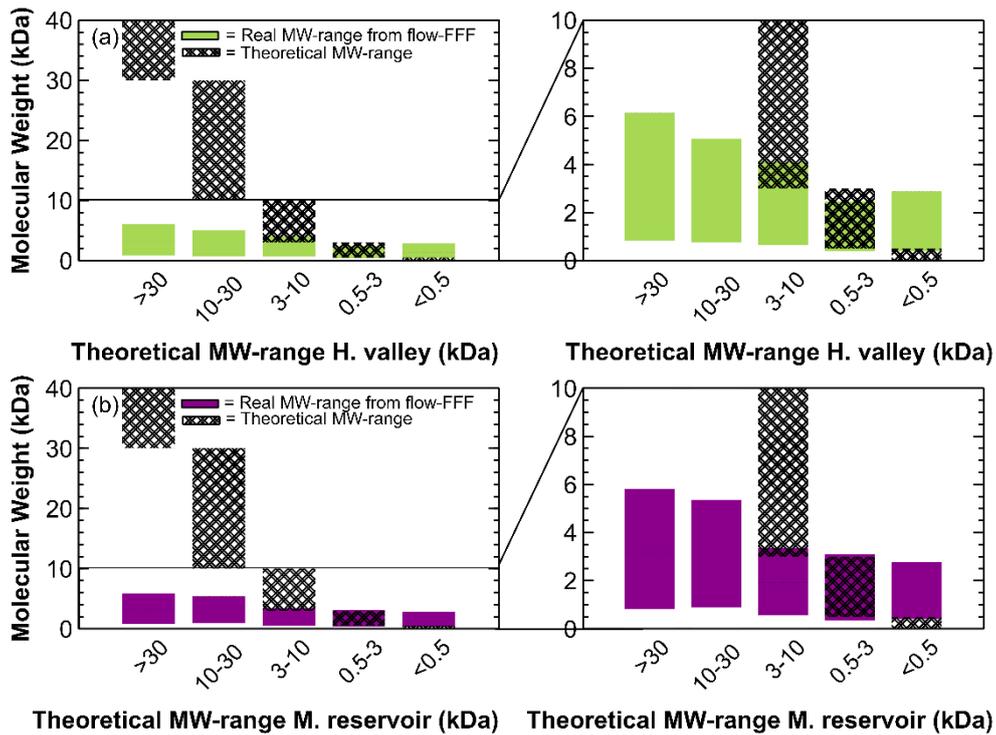
203 on respectively the permeate and the retentate side. Diafiltration is performed in each step to
 204 ensure a higher purity of the fractions (Yin et al., 2019).



205

206 **Fig. 1 (a)** Dead-end ultrafiltration membrane fractionation of natural organic matter into five fractions (F1-5).
 207 Their molecular weight range is based on the molecular weight cut-off of the membrane (presented in the upper
 208 right corner of the rectangle) (b) Crossflow membrane fractionation by Yin et al. (2019) using consecutive nano-
 209 (NF) and ultrafiltration (UF) processes to split organic matter present in seawater into biopolymers (F.BP), humic
 210 substances & building blocks (F.HS&BB) and low molecular weight molecules (F.LMW). Demineralized (DI) water is
 211 added during the process to increase the purity of the fractions. Reprinted from [Water Research, 159, Wenqiang
 212 Yin, Xin Li, Stanislaus Raditya Suwarno, Emile R. Cornelissen, Tzyy Haur Chong, Fouling behavior of isolated
 213 dissolved organic fractions from seawater in reverse osmosis (RO) desalination process, 385-396, copyright (2019)]
 214 with permission from Elsevier

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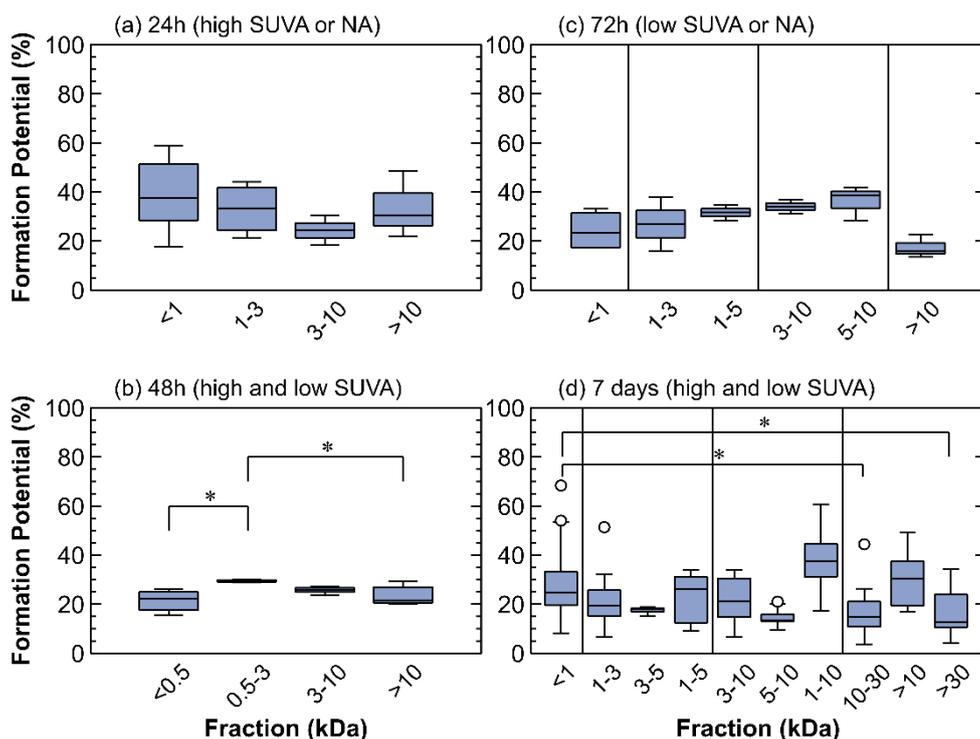
216

217 **Fig. 2** Visualization of the results from Assemi et al. (2004) where organic matter in water samples from (a) Hope
 218 valley and (b) Myponga reservoir was fractionated into 5 fractions by dead-end ultrafiltration membrane
 219 fractionation and subsequently analyzed by flow-field flow fractionation (Flow-FFF). Each fraction is plotted on the
 220 x-axis and their theoretical molecular weight (MW)-range is determined by the molecular weight cut-off of each
 221 membrane. This range is visualized by cross pattern bars plotted on the y-axis. Flow-field flow fractionation (Flow-
 222 FFF) was used to determine the real molecular weight-range of each fraction, which is shown by solid bars plotted
 223 on the y-axis. A magnification of (a) and (b) between 0 and 10 kDa is given on the right side of these graphs. It is
 224 clear that the real molecular weight range of a fraction can differ substantially from its theoretical range.
 225 Furthermore, the real molecular weight range of the fractions are largely overlapping, meaning that the
 226 separation of organic matter based on size was unsuccessful.

227 Although membrane fractionation is a relatively fast and cheap method through the use of
228 commercially available membranes, it seems to lack the ability to produce sharply separated
229 fractions. The two main causes could be (i) the molecular weight cut-off of a membrane is not strict
230 and (ii) dead-end cell operation causing fouling can influence the retention of all compounds.
231 Therefore, care should be taken when interpreting the results of different studies using ultrafiltration
232 fractionation, since it is not guaranteed that the fractions really contain the molecular weight range
233 as defined by the molecular weight cut-offs of the ultrafiltration membranes. A crossflow filtration
234 seems more reliable, since it reduces fouling and has the ability to pass the feedwater several times
235 over the membrane, allowing the gradual removal of the desired compounds with diafiltration. This
236 will however dilute the final concentrations in the membrane fractions. **The relationship between
237 membrane fractions and disinfection by-product formation is extensively studied and will be
238 discussed in the next section.**

239 3.2 Identification of membrane fractions involved in disinfection by-product 240 formation

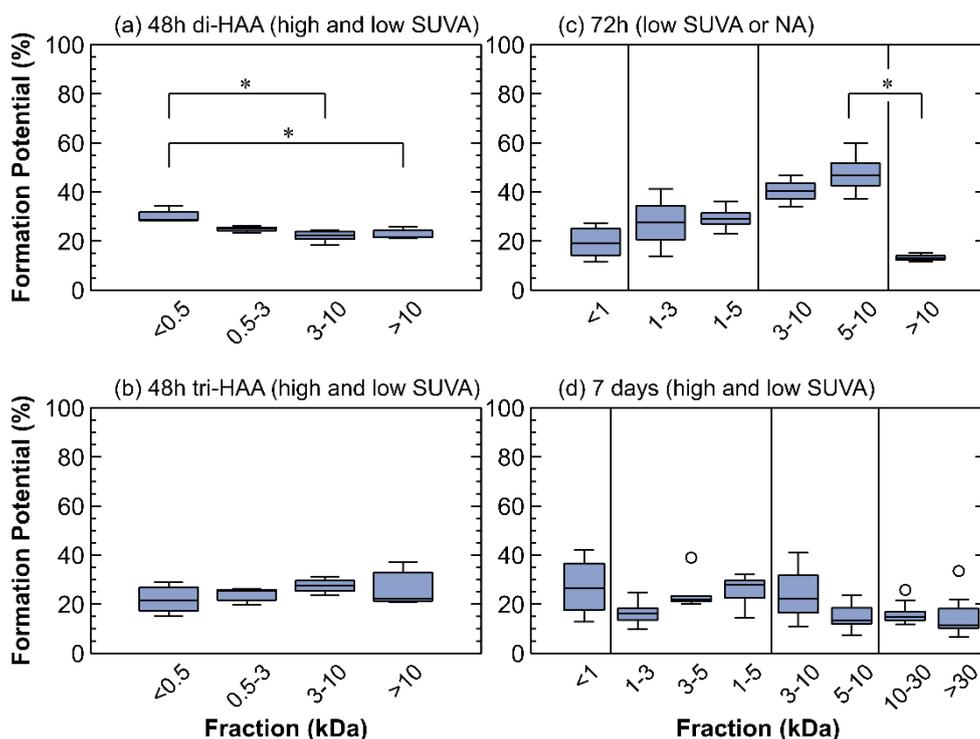
241 Fig. 3 represents the specific trihalomethane formation potential after different chlorination times
242 and different specific ultraviolet absorbance ($SUVA_{254}$) values in several membrane fractions (section
243 6 for Methods). $SUVA_{254}$ is defined as the absorbance of ultraviolet light at 254 nm divided by the
244 organic matter concentration (Ho et al., 2013). From this, it appears that the reactivity for
245 trihalomethane formation increases when the molecular weight of organic material decreases,
246 although the correlation remains weak. After 48 h with low chlorine dose or after 7 days with high
247 chlorine dose, there is a clear difference between the highest and lowest membrane fractions. Here,
248 the < 1 kDa fraction has significantly higher specific formation potential compared to the > 10 kDa
249 fraction. On the other hand, only a small, non-significative discrepancy is seen between the highest
250 (> 10 kDa) and lowest (< 1 kDa) membrane fractions after 24 h (low chlorine dose) or 72 h (high
251 chlorine dose). It seems that $SUVA_{254}$ has no influence on the results, since fractionated waters with
252 either high or low $SUVA_{254}$ give a same trend in specific trihalomethane formation potential (Fig.
253 3a,c).



254

255 **Fig. 3** Specific trihalomethane formation potential (%) in different membrane fractions after (a) 24h, high or not
 256 available (NA) **specific ultraviolet absorbance at 254 nm** (SUVA₂₅₄), low chlorine dose (5 water samples) (b) 48h,
 257 high and low SUVA₂₅₄, low chlorine dose (6 water samples) (c) 72h, low SUVA₂₅₄ or not available, high chlorine
 258 dose (5 water samples) and (d) 7 days, SUVA₂₅₄ is high, low or not available, high chlorine dose (29 water
 259 samples). * = statistical difference, ° = outlier. **The specific trihalomethane formation potential slightly increases**
 260 **towards smaller molecular weight fractions. SUVA₂₅₄ or chlorine dose seem not to have an influence on this trend.**

261 Moreover, di-halogenated acetic acid formation follows the same relationship as trihalomethanes
 262 between molecular weight and formation potential, since the < 1 kDa fraction has significantly higher
 263 formation potential compared to 3-10 kDa and > 10 kDa fraction (Fig. 4a). This trend is not visible at
 264 all for tri-halogenated acetic acid formation, where all 4 fractions have the same formation potential
 265 behavior (Fig. 4b). When overall specific haloacetic acid formation potential is measured, a small
 266 increase in reaction potential is seen after 7 days of reaction for lower molecular weight fractions,
 267 although it was not significant (Fig. 4d). However, after 72 h, an opposite trend is noticeable with a
 268 maximum formation potential in the 5-10 kDa fraction (Fig. 4c). No assessment of the effect of
 269 SUVA₂₅₄ could be made due to a lack of data. Table S1 provides the data collected for emerging
 270 disinfection by-products, but this dataset is too limited to draw any conclusion (Ge et al., 2020; Hua
 271 et al., 2015; Hua et al., 2020; Lin et al., 2014; Zhang et al., 2021; Zhang et al., 2020b).



272

273 **Fig. 4** Specific haloacetic acid formation potential (%) in different membrane fractions after (a) 48h, di-
 274 halogenated acetic acids (di-HAA), high and low specific ultraviolet absorbance at 254 nm (SUVA₂₅₄), low chlorine
 275 dose (6 water samples) (b) 48h, tri-halogenated acetic acids (tri-HAA), high and low SUVA₂₅₄, low chlorine
 276 dose (6 water samples) (c) 72h, low SUVA₂₅₄ or not available (NA), high chlorine dose (6 water samples) and (d)
 277 7 days, SUVA₂₅₄ is high, low or not available, high chlorine dose (14 water samples). * = statistical difference, ° = outlier.
 278 Specific di-halogenated acetic acid formation is higher towards lower molecular weight fractions, while all
 279 fractions have the same formation potential for tri-halogenated acetic acids. No correlation was established when
 280 all haloacetic acids are included.

281 Also in literature, conflicting trends between specific trihalomethane formation potential and
 282 molecular weight range are stated. For example, the specific formation potential is reported to
 283 increase when the molecular weight of the fractions decreases, while on the other hand authors
 284 have reported a peak in specific formation potential in medium molecular weight fractions. In
 285 contradiction to the above findings, increasing formation potential with increasing molecular weight
 286 have also been reported and some studies show no correlation at all between the formation
 287 potential and molecular weight. Conflicting conclusions exist as well for both specific di-halogenated
 288 and tri-halogenated acetic acid formation potentials and emerging disinfection by-products (An et al.,
 289 2017; Avsar et al., 2015; Chang et al., 2001; Chiang et al., 2002; Gang et al., 2003; Ge et al., 2020;
 290 Goslan et al., 2004; Hu et al., 2015; Hua and Reckhow, 2007b; Hua et al., 2015; Hua et al., 2020;
 291 Karapinar et al., 2014; Kitis et al., 2002; Lin et al., 2014; Liu et al., 2011; Özdemr, 2014; Pi et al., 2021;
 292 Pramanik et al., 2015; Wei et al., 2008a; Wei et al., 2008b; Xu et al., 2007; Xu et al., 2011; Zhang et
 293 al., 2021; Zhang et al., 2020b; Zhang et al., 2010; Zhang et al., 2018; Zhao et al., 2006; Zhao et al.,
 294 2009).

295 In addition, Hua et al. (2020) analyzed waters with both high and low SUVA₂₅₄ values, including
 296 commercial humic acid as high SUVA₂₅₄ source and a surface water as low SUVA₂₅₄ source. Here, high

297 molecular weight compounds (> 30 kDa) contributed the most to specific regulated and unregulated
298 disinfection by-product formation potential. Precursors from high SUVA₂₅₄ waters showed a clear
299 humic-acid like signal with high molecular weight, while precursors from low SUVA₂₅₄ waters showed
300 a high molecular weight protein-like signal. On the other hand, both high and low molecular weight
301 fractions have been indicated as having high regulated and unregulated disinfection formation
302 potential consisting of humic acid-like and/or soluble microbial by-product-like compounds (Hua et
303 al., 2007; Zhang et al., 2020b). The latter ones cover a wide range of molecular weight (0.5-50 kDa)
304 (Barker and Stuckey, 1999). Furthermore, Zhang et al. (2016) showed with commercial humic acids
305 that the formation of iodinated trihalomethanes increases with molecular weight.

306 The aforementioned SUVA₂₅₄ or molecular weight correlations were however not visible when data
307 from all papers were taken together. Regarding the previous discussion on overlapping fractions in
308 membrane fractionation (section 3.1), this could be an important drawback in the studies which
309 intended to discriminate disinfection by-product formation on molecular weight. It would be
310 beneficial to optimize the membrane fractionation approach. A possible starting point for this could
311 be the fractionation protocol developed by Yin et al. (2019) (section 3.1). Analyzing trihalomethanes
312 and haloacetic acid formation potentials on well-defined fractions might clarify the most important
313 natural organic matter precursors.

314 Another observation made in literature is that the lowest molecular weight fractions produce
315 relatively more brominated disinfection by-products and therefore, it has been stated that low
316 molecular weight compounds are more reactive towards bromine (Hu et al., 2015; Xu et al., 2007).
317 Nonetheless, the bromide-to-total organic carbon ratio in the different fractions will change
318 depending on the retention of both organics and bromide during membrane filtration. When the
319 concentration of bromide is adjusted to the initial concentration for all fractions, either the previous
320 statement is confirmed or no specific trend is seen in bromide incorporation for the different
321 fractions (Hua and Reckhow, 2007b; Kitis et al., 2002).

322 In summary, the relationship between molecular weight and disinfection by-product formation
323 appeared to be very weak. Alternatively, natural organic matter is split based on hydrophobicity
324 instead of size by the usage of resins. These different techniques will be elaborated in the next
325 section.

326 4 Resin fractionation

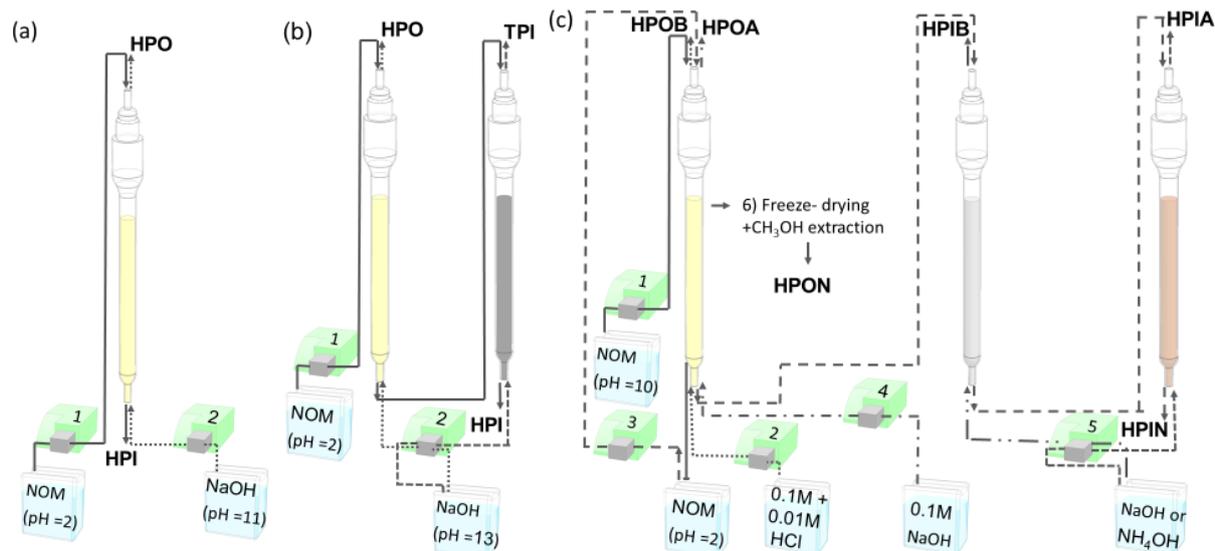
327 4.1 Principle of resin fractionation

328 In resin fractionation, a liquid sample is fed to a polymeric resin adsorbing organic matter which is
329 subsequently eluted using a solvent of suitable polarity (Minor et al., 2014). Aiken et al. (1979)
330 introduced this technique for the first time using commercially available non-polar XAD-resins. The

331 resins can be composed of styrene-divinylbenzene or methyl-methacrylate polymers (Daignault et
332 al., 1988; Kim and Yu, 2005). Several modifications have been made over the years to optimize this
333 method (Matilainen et al., 2011). XAD-8 and XAD-4 are the main resins used in the different
334 fractionation methods. Since XAD-8 is no longer commercially available, XAD-7HP, DAX-8 or C18 silica
335 resins have been used as alternatives. XAD-8 and DAX-8 show very comparable physical and chemical
336 properties and their comparability for aquatic use has been proven (Chow, 2006). XAD-7HP has the
337 same chemical structure as XAD-8 (polymethyl-methacrylate), but XAD-7HP has a larger surface area
338 and is more porous (Pan et al., 2016). XAD-4 is composed of non-ionic styrene divinylbenzene
339 polymer and C18 resins are composed of hydrocarbons bonded to a silica matrix and have generally
340 higher recoveries than XAD-resins (Minor et al., 2014).

341 The simplest resin fractionation method generates a hydrophobic and hydrophilic fraction using a
342 single XAD-8 resin at pH 2 (Fig. 5a). Adsorption onto XAD-resins occurs through aromatic π - electron
343 and hydrophobic interactions (Bond et al., 2009). Therefore, compounds that are not retained are
344 defined as hydrophilic compounds. The less hydrophilic compounds are adsorbed on the XAD-8 resin
345 and defined as the hydrophobic fraction (Aiken et al., 1979; Jung and Son, 2008; Kim and Yu, 2005;
346 Kim et al., 2006b; Kitis et al., 2002; Liang and Singer, 2003; Thurman and Malcolm, 1981). They are
347 eluted with sodiumhydroxide at pH 11. Increasing the pH will ionize carboxyl and phenolic hydroxyl
348 groups and desorb the hydrophobic compounds (Aiken et al., 1979).

349 An additional step has been added to this method by passing the hydrophilic fraction over a XAD-4
350 resin at pH 2 (Fig. 5b). The fraction that is not retained, is the hydrophilic (non-acid) fraction. The
351 fraction that is retained by XAD-4 and eluted at pH 13 with sodiumhydroxide or acetonitrile is called
352 the transphilic or hydrophilic acid fraction (Aiken et al., 1992; Croué, 2004; Golea et al., 2017; Hu et
353 al., 2015; Hua and Reckhow, 2007b; Hua et al., 2015; Leenheer et al., 1999; Li et al., 2014; Malcolm
354 and Maccarthy, 1992; Rho et al., 2019; Song et al., 2009; Tubić et al., 2013; Xu et al., 2007). The
355 hydrophobic fraction is retained in a similar way as in the previous method with XAD-8, only the pH
356 used to desorb the fraction is different (pH 11 vs. 13). A 100% effective elution at pH 13 is obtained
357 due to the (complete) ionization of carboxyl and phenolic hydroxyl groups and a near 100% carbon
358 recovery is obtained by co-current elution of a 75/25 acetonitrile/water mixture (Aiken et al., 1979;
359 Croué, 2004).



360

361 **Fig. 5** Resin fractionation schemes to split natural organic matter (NOM) based on hydrophobicity. The numbers
 362 on the pumps represent the sequence of adsorption-desorption. HPO = hydrophobic, HPI = hydrophilic, TPI =
 363 transphilic. A = acid, B = base, N = neutral. Yellow = XAD-8, XAD-7HP or DAX-8 resin; black = XAD-4 resin; orange =
 364 Duolite A7, IRA 93 or WA10 resin; grey = AG-MP-50, Dowex MSC resin (a) HPO-HPI fractionation, (b) HPO-TPI-HPI
 365 fractionation. Acetonitrile can also be used as desorbent instead of sodiumhydroxide, (c) HPO(A+B+N)-HPI(A+B+N)
 366 fractionation. The water solution is acidified to pH=2 after the first run

367 A very elaborate resin fractionation splits natural organic matter into six fractions: hydrophobic acids,
 368 bases, neutrals and hydrophilic acids, bases and neutrals (Fig. 5c). More detailed information on
 369 organic species present in the water is obtained with this fractionation, which can facilitate
 370 subsequent analysis in different research fields, such as disinfection by-product formation. The most
 371 common method is to pass the sample through the XAD-8 resin twice. After the first run at pH 10 or
 372 without pH adjustment, hydrophobic bases are recovered by desorption with hydrochloric acid,
 373 which protonates the basic compounds. The second run is performed at pH 2, after which
 374 hydrophobic acids are eluted with sodiumhydroxide. This is the same approach as in the previous
 375 methods to obtain the overall hydrophobic fraction. The hydrophobic neutral fraction is obtained by
 376 (freeze-) drying the XAD-8 resin and extracting the compounds from the resin with methanol. DAX-8
 377 and Bond Elute ENV cartridges (styrene-divinyl benzene) are also used for this purpose.

378 Subsequently, the hydrophilic compounds are split into acids, bases and neutrals by the use of ion
 379 exchange resins. The water sample at pH 2 is introduced to a cation exchange resin (AG-MP-
 380 50/Dowex MSC/Strata X-C) which retains the hydrophilic base compounds (Chang et al., 2000; Chang
 381 et al., 2001; Chen et al., 2008; Goss and Gorczyca, 2013; Kanokkantapong et al., 2006b; Lamsal et al.,
 382 2012; Leenheer, 1981; Marhaba et al., 2003; Ratpukdi et al., 2009; Zhang et al., 2009; Zhang et al.,
 383 2008). These are all strong acid, sulfonated resins with different backbone structures. AG-MP-50
 384 consists of a polystyrene backbone, while Dowex MSC has a styrene-divinylbenzene structure
 385 (Leenheer, 1981; Meyer et al., 2020; Ratpukdi et al., 2009). A weak anion exchange resin
 386 (WA10/Duolite A7/IRA 93/Strata X-AW) retains the hydrophilic acid fraction at pH 2, while the

387 hydrophilic neutral compounds are not retained. The anion exchange resins all consist of amine
388 functionality (primary, secondary or tertiary) with different backbones, going from polystyrene, to
389 acrylic polymers and even phenol-formaldehyde condensation matrices. Duolite A7 suffers from
390 severe resin bleeding (Kananpanah et al., 2009; Leenheer, 1981; Marhaba et al., 2003; Miyazaki and
391 Nakai, 2011; Ratpukdi et al., 2009). Ammoniumhydroxide or sodiumhydroxide are used to desorb
392 both fractions. Ammoniumhydroxide returns the resins in their hydrogen (cation exchange resin) or
393 free-base form (anion exchange resin) (Chang et al., 2000; Chang et al., 2001; Chen et al., 2008; Goss
394 and Gorczyca, 2013; Kanokkantapong et al., 2006b; Lamsal et al., 2012; Leenheer, 1981; Marhaba et
395 al., 2003; Ratpukdi et al., 2009; Zhang et al., 2009; Zhang et al., 2008).

396 Resin fractionation is a very common, relatively cheap and widely applied technique with the use of
397 commercially available resins. The method can be either fast (into hydrophobic-hydrophilic) or time-
398 consuming (into their respective acids, bases and neutrals). It simultaneously concentrates and
399 fractionates organic matter, but there have been some doubts about possible changes in the
400 chemical and/or physical nature of the water matrix due to the extreme pH-alterations (Matilainen
401 et al., 2011; Swietlik et al., 2004). Furthermore, different column capacity factors are used among
402 different authors. This factor is defined as

$$k' = \frac{\text{mass of solute sorbed on the resin}}{\text{mass of solute dissolved in water}}$$

403 and is directly proportional to the volume of water applied on a certain resin volume (Leenheer,
404 1981). The higher the value, the lower the percentage of hydrophobic compounds that is retained on
405 a XAD-8 column for one water sample which can influence further assessments (Song et al., 2009).
406 Also, flow rate and bed height of the column influence the adsorption equilibrium as both
407 parameters change the contact time between adsorbate and adsorbent (Patel, 2019). These
408 parameters are, however, very often lacking in the method sections.

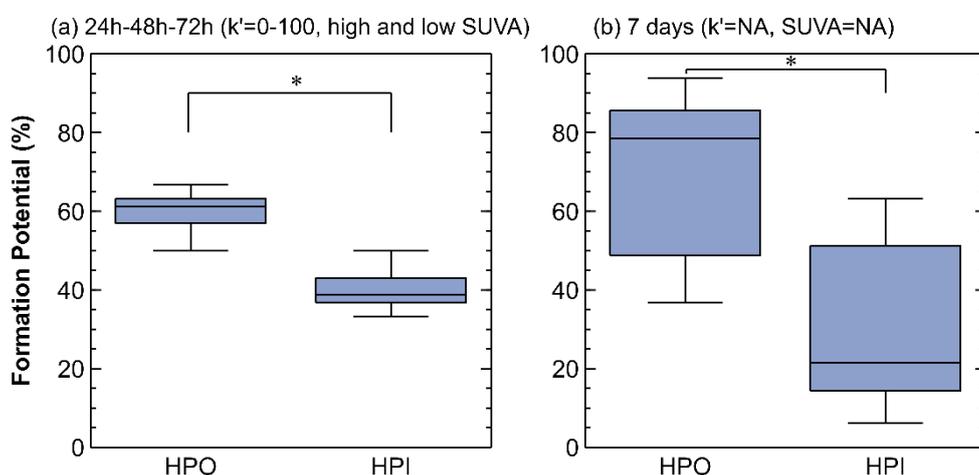
409 **In general, studies investigating disinfection by-product precursors with resin fractionation use one**
410 **of the abovementioned resins and fractionation techniques. The only parameter that varies**
411 **substantially is the column capacity factor which will therefore be considered in the next section**
412 **when comparing the results of these studies.**

413 4.2 Resin fractions involved in disinfection by-product formation

414 4.2.1 Trihalomethanes

415 When looking at the simplest fractionation technique, namely splitting natural organic matter into a
416 hydrophobic and hydrophilic fraction, results are quite consistent (Fig. 6, section 6 for Methods). The
417 hydrophobic fraction produces the highest specific trihalomethane formation potential regardless of
418 chlorination time and SUVA₂₅₄ ($k' = 100$ or undefined). Specific ultraviolet absorbance (SUVA₂₅₄) is

419 defined as the absorbance of ultra violet light at 254 nm divided by the organic matter concentration
 420 (Ho et al., 2013). Up to 72 h and low chlorine dose, hydrophobic moieties have 20 % higher specific
 421 formation potential compared to the hydrophilic fraction (Fig. 6a). After 7 days, the difference
 422 between the medians even increases to 60 %, although the boxplots themselves show more
 423 variability (Fig. 6b). After 7 days reaction time with high chlorine dose, both fast and slow reacting
 424 compounds will form trihalomethanes, thereby scattering the data (Chang et al., 2001; Chiang et al.,
 425 2002; Chiang et al., 2009; Galapate et al., 2001; Goss et al., 2017; Hyung Kim and Yu, 2005; Imai et al.,
 426 2003; Jung and Son, 2008; Kim et al., 2006a; Kim and Yu, 2005; Kitis et al., 2002; Kueseng et al., 2011;
 427 Liang and Singer, 2003; Musikavong et al., 2013). The hydrophobic fraction has previously been
 428 implicated as the primary source of trihalomethane precursors with some exceptions (Chow et al.,
 429 2005). The discrepancies have been allocated to differences in chlorination methods, but no
 430 thorough assessment was made.



431
 432 **Fig. 6** Specific trihalomethane formation potential (%) in the hydrophobic (HPO) and hydrophilic (HPI) fraction
 433 after (a) 24h-48h-72h, high and low specific ultraviolet absorbance at 254 nm ($SUVA_{254}$), the column capacity
 434 factor (k') is between 0-100, but in most cases 100, low chlorine dose (25 water samples) (b) 7 days, $SUVA_{254}$ and
 435 k' in general not available (NA), high chlorine dose ($SUVA_{254}$ is 3x high, 1x low and k' is 2x 50 and 1x 100) (16 water
 436 samples). * = statistical difference. Hydrophobic compounds clearly have a higher specific trihalomethane
 437 formation potential compared to hydrophilic compounds irrespective of $SUVA_{254}$ or k' .

438 When the hydrophilic fraction is passed over the XAD-4 resin to generate the transphilic (or
 439 hydrophilic acid) fraction and the hydrophilic non-acid fraction, the situation becomes more
 440 complex, because the $SUVA_{254}$ value of the raw water influences the specific trihalomethane
 441 formation potential of the different fractions (Fig. 7). When $SUVA_{254}$ of the raw water is high
 442 ($> 2 \text{ L}/(\text{mg}\cdot\text{m})$), the hydrophobic and transphilic fraction have a similar reaction potential ($\sim 30\%$) to
 443 trihalomethane formation at short reaction times and low chlorine dose, while hydrophobic
 444 compounds have significantly higher specific trihalomethane formation potential compared to the
 445 transphilic and hydrophilic fraction at long reaction times with high chlorine dosage (Fig. 7a,c).
 446 Conversely, when the $SUVA_{254}$ level is below $2 \text{ L}/(\text{mg}\cdot\text{m})$, hydrophilic organics have equally important

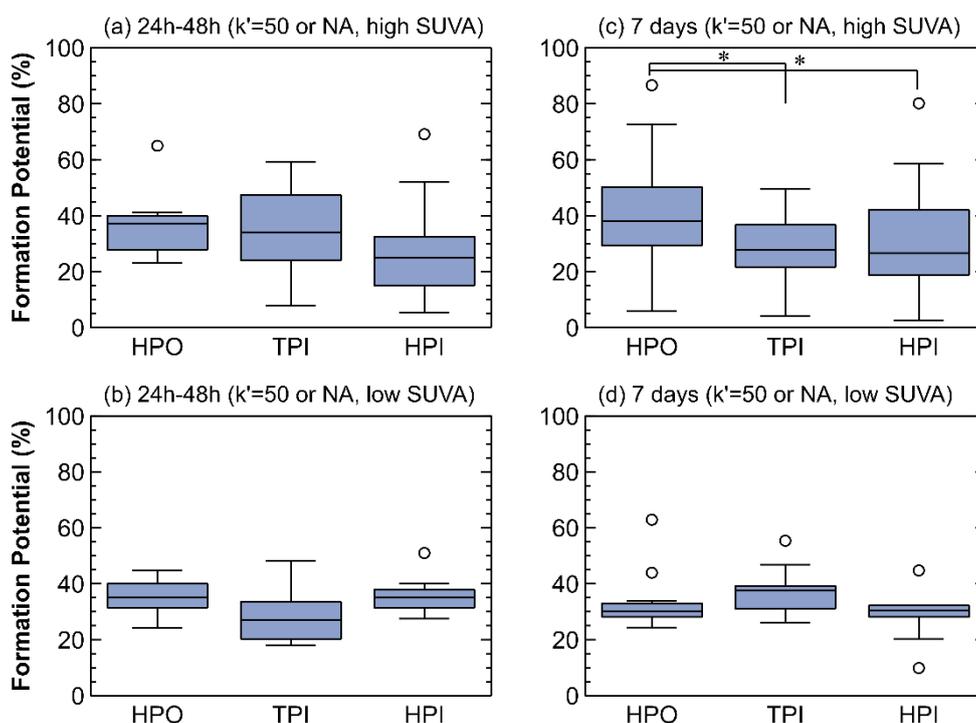
447 trihalomethane formation potential as hydrophobic organics at short reaction times (~40 %), while
448 transphilic organic matter seems slightly more reactive after 7 days of reaction and high chlorine
449 dose (Fig. 7b,d) (Agbaba et al., 2014; Chowdhury et al., 2008; Fang et al., 2021; Goslan et al., 2002;
450 Goslan et al., 2004; Hanigan et al., 2013; Hu et al., 2015; Hua and Reckhow, 2007b; Hua et al., 2015;
451 Li et al., 2014; Lin and Wang, 2011; Lin et al., 2014; Liu et al., 2011; Molnar et al., 2012a; Molnar et
452 al., 2013; Molnar et al., 2012b; Musikavong et al., 2016; Niu et al., 2015; Phetrak et al., 2016; Pi et al.,
453 2021; Roccaro et al., 2014; Smith and Al Qabany, 2009; Tubić et al., 2013; Wang et al., 2013; Wei et
454 al., 2008a; Wei et al., 2008b; Xu et al., 2007; Xue et al., 2010; Zhang et al., 2021; Zhao et al., 2013;
455 Zhi-sheng et al., 2009).

456 Overall, the hydrophobic fraction is an important contributor to trihalomethane formation at high
457 SUVA₂₅₄, especially at long reaction times with high chlorine dosage, while both hydrophobic and
458 hydrophilic compounds are important at low SUVA₂₅₄. This observation could not be verified in the
459 previous fractionation, since only 5 water samples were found to have low SUVA₂₅₄ values. From
460 these 5 samples, 4 of them were chlorinated with a low dose between 24 and 72 h. Here, the ratio of
461 60 % trihalomethane formation from the hydrophobic fraction and 40 % from the hydrophilic
462 fraction was valid, except for one sample that had a ratio of 53 % versus 47 %. The only water sample
463 analyzed after 7 days and high chlorine dose showed a ratio of only 37 % trihalomethane formation
464 from hydrophobic compounds and 63 % from hydrophilic compounds (Chiang et al., 2009; Hyung Kim
465 and Yu, 2005; Imai et al., 2003; Kim et al., 2006a; Kim and Yu, 2005).

466 Disinfection by-product formation investigated with natural organic matter surrogates has shown
467 that activated aromatic moieties in the presence of an electron-donating and ortho-para directing
468 group have high rate constants towards chlorine reactivity, because hypochlorous acid (an
469 electrophile) preferentially reacts with electron-rich functionalities in organic molecules. These
470 moieties will also contribute to high SUVA₂₅₄ values and reside in the hydrophobic fraction (Bond et
471 al., 2012a; Bond et al., 2009). When the SUVA₂₅₄ value is low, other chemical functionalities with
472 lower reactivities, such as amino acids or carbohydrates (hydrophilic compounds), will become
473 important especially after longer reaction time and high chlorine dose (Bond et al., 2012a).

474 Nonetheless, the behavior of the transphilic fraction for both high and low SUVA₂₅₄ conditions is less
475 clear. This fraction has been characterized as having greater heteroatom and carboxyl content than
476 the hydrophobic fraction, but also as having a number of similar properties with the hydrophobic
477 fraction (Aiken et al., 1992). The C/O, C/H and C/N atomic ratios gradually decrease from
478 hydrophobic to transphilic to hydrophilic (Croué, 2004). Furthermore, fractionation of surrogates
479 with different polarities could not identify molecules having clear transphilic character. Surrogates
480 ending up in the transphilic fraction were evenly distributed in either the hydrophobic or hydrophilic
481 fraction (Bond et al., 2009). This implies that depending on the natural organic matter composition of

482 the water source, the transphilic fraction can have more hydrophobic or hydrophilic character, which
 483 will influence its specific trihalomethane formation potential.
 484 Within the hydrophobic fraction in both resin fractionation methods, humic acids are the most
 485 important precursors. Humic acids precipitate when acidifying the hydrophobic fraction to pH = 1,
 486 while fulvic acids remain dissolved (Agbaba et al., 2014; Goslan et al., 2002; Goslan et al., 2004; Jung
 487 and Son, 2008; Molnar et al., 2012a; Molnar et al., 2012b; Tubić et al., 2013; Zhi-sheng et al., 2009).



488
 489 **Fig. 7** Specific trihalomethane formation potential (%) in the hydrophobic (HPO), transphilic (TPI) and hydrophilic
 490 (HPI) fraction after **(a)** 24h-48h, high specific ultraviolet absorbance at 254 nm (SUVA₂₅₄), the column capacity
 491 factor k' is 50 (1x 100) or not available (NA), low chlorine dose (13 water samples) **(b)** 24h-48h, low SUVA₂₅₄, k' is
 492 50 or not available, low chlorine dose (7 water samples) **(c)** 7 days, high SUVA₂₅₄, k' is 50 or not available, high
 493 chlorine dose (39 water samples) and **(d)** 7 days, low SUVA₂₅₄, k' is 50 or not available, high chlorine dose (11
 494 water samples). * = statistical difference, ° = outlier. **When the SUVA₂₅₄ of the raw water is greater than 2**
 495 **L/(mg·m), the HPO fraction contributes the most to trihalomethane formation, especially at long chlorination time**
 496 **with high chlorine dose. When the SUVA₂₅₄ is below 2, the hydrophobic and hydrophilic fraction have equal**
 497 **trihalomethane formation potential. The contribution of the transphilic fraction is very variable**

498 Limited data was found for specific trihalomethane formation potential after fractionation of natural
 499 organic matter into hydrophobic and hydrophilic acids, bases and neutrals (Fig. S1). At short reaction
 500 times, the hydrophobic acid fraction seems equivalent to the hydrophilic base fraction, although the
 501 dataset was too small to find statistical differences. The SUVA₂₅₄ was low, so it confirms the
 502 statement that both hydrophobic and hydrophilic fractions are important in low SUVA₂₅₄ waters, and
 503 possibly, in more detail the hydrophobic acid and hydrophilic base fraction. At long chlorination
 504 times, however, it is the hydrophobic and hydrophilic base fraction and to a lesser extent the
 505 hydrophobic neutral fraction that have the highest specific trihalomethane formation potential,
 506 especially compared to hydrophilic neutrals (Chang et al., 2000; Chen et al., 2008; Fan et al., 2013;

507 Goss and Gorczyca, 2013; Lamsal et al., 2012; Lin et al., 2010; Marhaba and Van, 2000;
508 Panyapinyopol et al., 2005a; Panyapinyopol et al., 2005b; Rakruam and Wattanachira, 2014; Sharma
509 et al., 2021; Włodyka-Bergier and Bergier, 2011; Yee et al., 2009; Yee et al., 2006). Bases are defined
510 as electron donors, thereby promoting the reaction with the electron poor hypochlorous acid (Bond
511 et al., 2012a). Furthermore, hydrophilic bases have been characterized as amide-like compounds,
512 while the hydrophilic neutral fraction mainly contains lignin and lipids (Wang et al., 2019). From Fig.
513 S1, there is thus an indication that lignin and lipids are recalcitrant to the formation of
514 trihalomethanes, while amide-like compounds might be important precursors. The occurrence of the
515 hydrophobic acid fraction is less straightforward, however, this is only based on 3 water samples.
516 The column capacity factor k' seems to have no influence on the results. Where the factor k' is 100 in
517 the hydrophobic-hydrophilic fractionation, it is 50 in the hydrophobic-transphilic-hydrophilic
518 fractionation. However, in the latter resin technique, data was found where both values have been
519 used during a 72h chlorination time with high chlorine dose (Fig. S2). Changing k' from 50 to 100 will
520 result in less adsorption of hydrophobic and transphilic compounds on XAD-8 and XAD-4 respectively
521 and this results into a changing trend in specific trihalomethane formation potential from the
522 hydrophobic fraction as most important precursor (Fig. S2a) to the hydrophilic fraction (Fig. S2b) (Liu
523 et al., 2011; Pi et al., 2021; Roccaro et al., 2014; Song et al., 2009; Zhang et al., 2021). So, although
524 the column capacity factor k' value did not affect the comparison between two fractionation
525 techniques, it stays important to be aware of this value at all times.

526 Finally, the hydrophilic fraction seems more sensitive to the formation of brominated
527 trihalomethanes (Agbaba et al., 2014; Chiang et al., 2009; Goss and Gorczyca, 2013; Hu et al., 2015;
528 Hua and Reckhow, 2007b; Kitis et al., 2002; Li et al., 2014; Liang and Singer, 2003; Molnar et al.,
529 2013; Molnar et al., 2012b; Musikavong et al., 2013; Musikavong et al., 2016; Niu et al., 2015;
530 Panyapinyopol et al., 2005a; Panyapinyopol et al., 2005b; Tubić et al., 2013; Włodyka-Bergier and
531 Bergier, 2011; Xu et al., 2007). In this regard, it is important to keep the same bromide-to-total
532 organic carbon ratio in all fractions. XAD-resins are non-ionic resins thereby not retaining ions (Aiken
533 et al., 1979; Daignault et al., 1988). Most of the bromide ions will therefore elute with the hydrophilic
534 fraction. These bromide ions will compete with organic carbon in the reaction with chlorine (rate
535 constant $k(\text{HOCl}/\text{Br}^-) = 1550 \cdot 1/\text{Ms}$) to produce bromine, which subsequently reacts with the total
536 organic carbon to produce brominated disinfection by-products (Criquet and Allard, 2021). Bromine
537 reactions towards phenolic moieties, which are important constituents of natural organic matter, are
538 up to three orders of magnitude greater than for chlorine. This higher reactivity explains the
539 tendency of brominated disinfection by-product formation even for a low bromide concentration
540 (Criquet et al., 2015; Heeb et al., 2014). When the bromide-to-total organic carbon ratio is adjusted
541 in all fractions, hydrophilic moieties are still more reactive towards bromine. This implies that

542 bromination occurs with aliphatic precursors while chlorination is more related to aromatic
543 precursors (Hua and Reckhow, 2007b; Kitis et al., 2002; Liang and Singer, 2003).

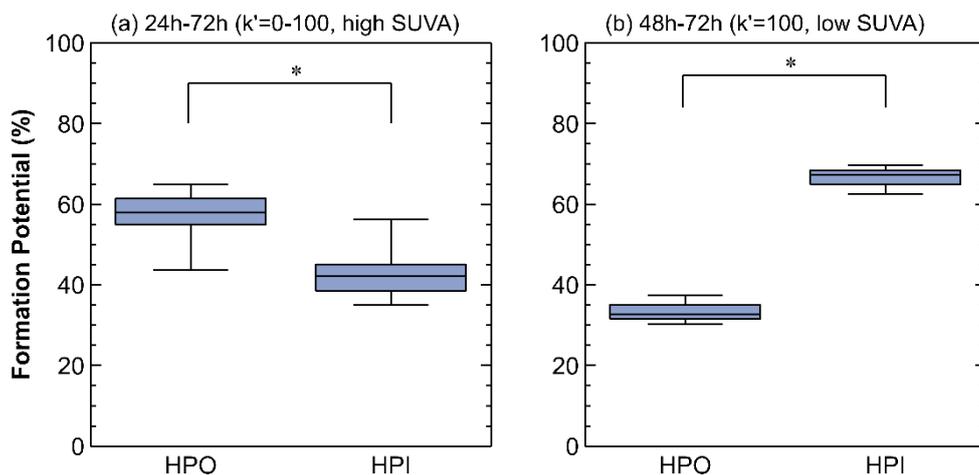
544 In summary, hydrophobic compounds produce the highest specific trihalomethane formation
545 potential, regardless of SUVA₂₅₄ or chlorination time, while hydrophilic compounds cannot be
546 ignored when the SUVA₂₅₄ of the raw water is low. Finally, base compounds are identified as one of
547 the most important precursors for trihalomethane formation. Haloacetic acids, as the second
548 regulated disinfection by-product family, have also been the focal point in research with resin
549 fractionation and results from these studies will be discussed in the next section.

550 4.2.2 Haloacetic acids

551 Fig. 8 shows the results from the hydrophobic-hydrophilic fractionation. As for the trihalomethanes,
552 the hydrophobic fraction has 60 % contribution to the total specific haloacetic acid formation
553 potential, while this is 40 % for the hydrophilic fraction at shorter reaction times, low chlorine dose
554 and high specific ultraviolet absorbance (SUVA₂₅₄) (Fig. 8a, section 6 for Methods) (Jung and Son,
555 2008; Kitis et al., 2002; Liang and Singer, 2003). SUVA₂₅₄ is defined as the absorbance of ultraviolet
556 light at 254 nm divided by the organic matter concentration (Ho et al., 2013). Two water samples
557 analyzed after 7 days and high chlorine concentrations also showed around 89% specific formation
558 potential from the hydrophobic fraction compared to only 11% from the hydrophilic fraction (Chang
559 et al., 2001; Chiang et al., 2002). On the contrary, three water samples with low SUVA₂₅₄ showed that
560 hydrophilic compounds have by far the highest reaction potential at short reaction times and low
561 chlorine dose (Fig. 8b) (Hyung Kim and Yu, 2005; Kim et al., 2006a; Kim and Yu, 2005).

562 Furthermore, in the hydrophobic-transphilic-hydrophilic fractionation, the hydrophobic and
563 hydrophilic fraction are significantly different from the transphilic fraction, but not significantly
564 different with each other at low SUVA₂₅₄, especially after 7 days of chlorination time with high
565 chlorine dose (Fig. 9). Where the hydrophilic fraction has almost 30% higher specific haloacetic acid
566 formation potential compared to the hydrophobic fraction when organic matter is split into
567 hydrophobic-hydrophilic only (Fig. 8b), hydrophobic and hydrophilic compounds contribute both to
568 30-40% of the total specific haloacetic acid formation potential when the fractionation is done into
569 hydrophobic-transphilic-hydrophilic (Fig. 9b,d) (Fang et al., 2021; Li et al., 2014; Niu et al., 2015). This
570 might be explained by the different column capacity factors k' used between the 2 fractionation
571 techniques ($k'=100$ vs. $k'=50$). Limited data after 72h chlorination time with high chlorine dose shows
572 that the contribution of the hydrophilic fraction becomes higher when this k' -factor changes from 50
573 to 100 which is in agreement with the higher reaction potential seen for hydrophilic compounds in
574 the hydrophobic-hydrophilic fractionation (Fig. S3) (Liu et al., 2011; Pi et al., 2021; Roccaro et al.,
575 2014; Zhang et al., 2021).

576 Waters fractionated into hydrophobic-transphilic-hydrophilic moieties with high $SUVA_{254}$ shows that
 577 the hydrophobic fraction has a higher formation potential to some degree when comparing the
 578 medians, although not significant (Fig. 9a,c). The transphilic fraction is in general the least important
 579 fraction to specific haloacetic acid formation potential (Chowdhury et al., 2008; Fang et al., 2021;
 580 Hanigan et al., 2013; Karapinar et al., 2014; Li et al., 2014; Molnar et al., 2012a; Qadafi et al., 2021;
 581 Roccaro et al., 2014; Tubić et al., 2013; Wang et al., 2013; Zhao et al., 2013).

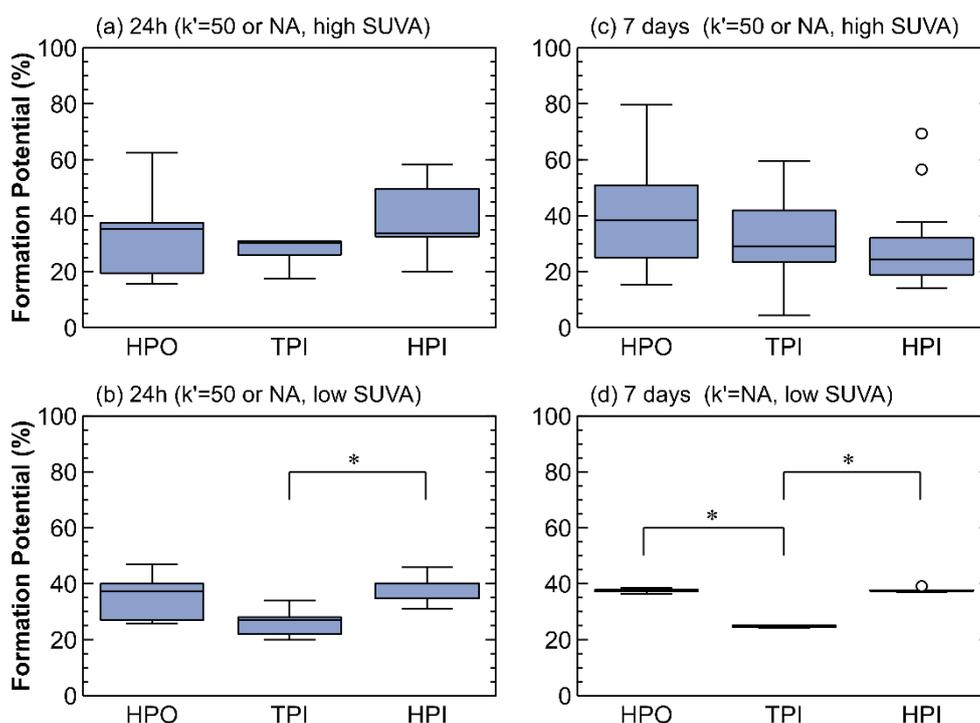


582
 583 **Fig. 8** Specific haloacetic acid formation potential (%) in the hydrophobic (HPO) and hydrophilic (HPI) fraction after
 584 (a) 24h-72h, high specific ultraviolet absorbance at 254 nm ($SUVA_{254}$), column capacity factor k' is between 0-100,
 585 but in most cases 100, low chlorine dose (15 water samples) (b) 48h-72h, low $SUVA_{254}$, k' is 100, low chlorine dose
 586 (3 water samples). * = statistical difference. **The hydrophobic fraction has significantly higher specific haloacetic**
 587 **acid formation potential compared to the hydrophilic fraction when $SUVA_{254}$ is high, while the opposite is seen**
 588 **when $SUVA_{254}$ of the raw water is low**

589 Data for the fractionation of the hydrophobic and hydrophilic fraction into their acids, bases and
 590 neutrals is limited to 72 h and 7 days of chlorination, high chlorine dose and 7 water samples (Fig.
 591 S4). The bases seem to have a slightly higher influence in specific haloacetic acid formation potential
 592 compared to the other fractions which is in agreement with the preference of the electrophilic
 593 hypochlorous acid to react with bases (Bond et al., 2012a; Chen et al., 2008; Fan et al., 2013;
 594 Kanokkantung et al., 2006a; Kanokkantung et al., 2006b; Kanokkantung et al., 2006c; Lamsal
 595 et al., 2012; Marhaba and Van, 2000).

596 Some research evaluated the formation of di-halogenated and tri-halogenated acetic acids
 597 separately (Fig. S5). The formation potential of the hydrophobic fraction for tri-halogenated acetic
 598 acids is significantly (~20 %) higher compared to the hydrophilic and transphilic fraction independent
 599 from the column capacity value (Fig. S5c,d). On the other hand, di-halogenated acetic acid formation
 600 potential is 20% higher in the hydrophobic fraction at high $SUVA_{254}$ and column capacity factor k' of
 601 100, while the hydrophilic fraction has the highest reaction potential at high and low $SUVA_{254}$ and k' -
 602 factor of 50 (Fig. S5a,b). It has been stated that dichloroacetic acid and trichloroacetic acid follow a
 603 different reaction pathway and that trichloroacetic acid and trihalomethanes are generated by

604 common intermediates. This has been concluded by surrogate analysis, where trichloroacetic acid
 605 precursors tend to be more hydrophobic and dichloroacetic acid precursors have more aliphatic
 606 structures (Bond et al., 2012a). These statements could not be completely confirmed with the
 607 collected data. However, it should be noted that these data were drawn from three different papers
 608 only and more research should be done to clarify these assumptions (Hua and Reckhow, 2007b; Hua
 609 et al., 2015; Liang and Singer, 2003).



610
 611 **Fig. 9** Specific haloacetic acid formation potential (%) in the hydrophobic (HPO), transphilic (TPI) and hydrophilic
 612 (HPI) fraction after **(a)** 24h, high specific ultraviolet absorbance at 254 nm (SUVA₂₅₄), column capacity factor k' is
 613 50 (1x 100) or not available (NA), low chlorine dose (5 water samples) **(b)** 24h, low SUVA₂₅₄, k' is 50 or not
 614 available, low chlorine dose (5 water samples) **(c)** 7 days, high SUVA₂₅₄, k' is 50 or not available, high chlorine dose
 615 (12 water samples) and **(d)** 7 days, low SUVA₂₅₄, k' is not available, high chlorine dose (5 water samples). * =
 616 statistical difference, ° = outlier. **Data from (c) suggest that hydrophobic moieties have slightly higher tendency to**
 617 **form haloacetic acids when the SUVA₂₅₄ of the raw water is high (>2 L/(mg·m)). Conversely, at low SUVA₂₅₄ values,**
 618 **both hydrophobic and hydrophilic moieties have equal and consistently higher specific haloacetic acid formation**
 619 **potential compared to the transphilic fraction.**

620 Furthermore, some data on bromide incorporation show a higher reactivity of hydrophilic fractions
 621 to produce brominated haloacetic acids (Hua and Reckhow, 2007b; Kitis et al., 2002; Li et al., 2014;
 622 Liang and Singer, 2003; Molnar et al., 2012a; Niu et al., 2015; Qadafi et al., 2021; Tubić et al., 2013;
 623 Włodyka-Bergier and Bergier, 2011).

624 To summarize, the precursors of haloacetic acids are found to be very similar to the precursors of
 625 trihalomethanes. They have hydrophobic character when SUVA₂₅₄ is high, although less pronounced
 626 than for the trihalomethanes, but have both hydrophobic and hydrophilic origin with SUVA₂₅₄ is low.

627 While chlorination time does not affect the outcome, there is an indication that the column capacity
 628 factor does change the formation potential behavior in the different fractions. **Besides the studies on**

629 regulated disinfection by-products, more attention arose in the last years to assess the precursors of
630 emerging disinfection by-products and the results of these studies will be presented in the final
631 section.

632 4.2.3 Emerging disinfection by-products

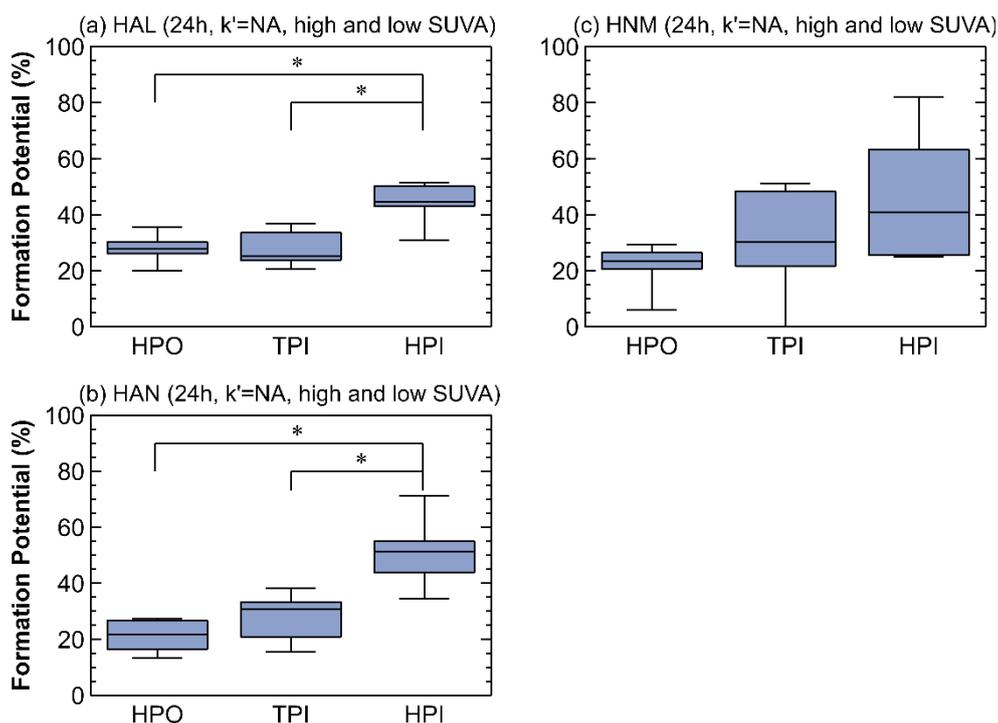
633 Emerging or unregulated disinfection by-products, such as haloacetamides, haloacetonitriles,
634 nitrosamines or haloketones, have received increased attention due to their higher toxicity
635 compared to regulated disinfection by-products (Wagner and Plewa, 2017). However, studies on the
636 formation of these by-products in different membrane or resin fractions with chlorine are nowadays
637 still limited. Most research focused on the formation of emerging disinfection by-products after
638 chloramination. Chloramine can significantly reduce the formation of trihalomethanes and tri-
639 halogenated acetic acids, but will greatly increase the formation of emerging nitrogenous
640 disinfection by-products such as N-nitrosodimethylamine (Chu et al., 2010; Hua and Reckhow, 2007a;
641 Lin et al., 2014; Wang et al., 2013).

642 A small number of studies focused on the formation of emerging disinfection by-products in resin
643 fractions disinfected with chlorine, *i.e.* haloacetamides, haloacetonitriles, halonitromethanes, halo-
644 aldehydes and haloketones. Insufficient data was collected for the last family to discuss a trend.
645 Studies on emerging disinfection by-products are most often executed with high chlorine dose even
646 at short reaction times, possibly because they are formed in very low concentrations during drinking
647 water disinfection (Richardson et al., 2007).

648 Despite chlorination time, dose or specific ultra violet absorbance ($SUVA_{254}$), hydrophilic compounds
649 clearly have a higher tendency to form emerging disinfection by-products (section 6 for Methods)
650 (Ho et al., 2013). $SUVA_{254}$ is calculated by dividing the ultraviolet absorbance at 254 nm by the
651 organic matter concentration. Fig. 10 and Figure S6 show a specific formation potential that is 20-
652 80 % higher for the hydrophilic fraction compared to the hydrophobic or transphilic fraction for most
653 families included (Fang et al., 2021; Ge et al., 2020; Hu et al., 2015; Hu et al., 2010; Hua et al., 2015;
654 Lin et al., 2014; Molnar et al., 2013; Molnar et al., 2012b; Roccaro et al., 2014; Tan et al., 2017; Zhang
655 et al., 2020a; Zhang et al., 2021). Halonitromethanes show no significant difference between the
656 formation potentials of all 3 fractions, despite the aspect of the graph (Fig. 10c). This is supported by
657 studies performing disinfection by-product formation tests on surrogates. Proteinaceous material
658 together with amino acids have been identified as haloacetonitrile precursors, while haloacetamides
659 can also be formed through the hydrolysis of haloacetonitriles. However, studies on hydrophilic
660 surrogates showed very low yield for trichloronitromethane, except for glycine (Bond et al., 2012b).

661 The influence of the column capacity factor k' stays inconclusive, because either a k' -factor of 50 is
662 used or the value is missing in the studied papers. There is a small indication that the value is less
663 important in the analysis of emerging disinfection by-products, since hydrophilic compounds also had

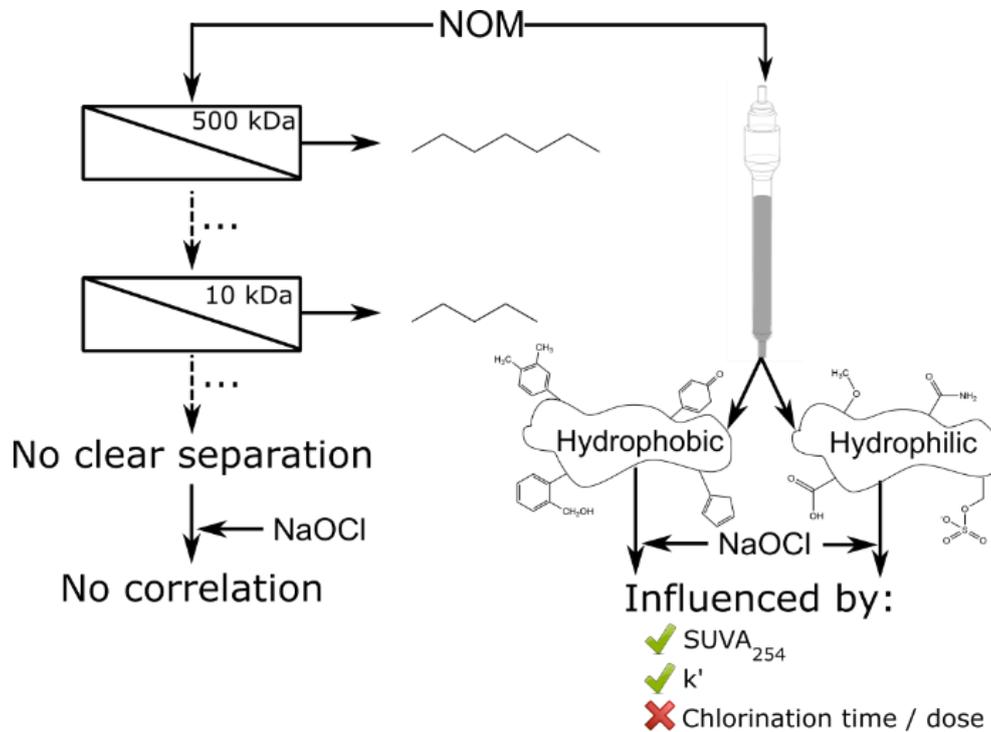
664 the highest contribution in a water sample with a k' of 100 for haloacetonitriles and 2 water samples
 665 with a k' of 15 for halonitromethane (Hu et al., 2010; Roccaro et al., 2014). Furthermore, elaborate
 666 resin fractionation in acids, bases and neutrals is hardly executed for emerging disinfection by-
 667 products. The results for haloacetonitrile, halo-aldehyde and trichloronitromethane are presented in
 668 Fig. S7, but no statistical differences or trends could be highlighted (Chu et al., 2010; Fan et al., 2013;
 669 Włodyka-Bergier and Bergier, 2011). In synopsis, emerging disinfection by-products clearly have
 670 hydrophilic precursors regardless of $SUVA_{254}$, chlorination time or dose.
 671



672
 673 **Fig. 10** Specific disinfection by-product formation potential (%) in the hydrophobic (HPO), transphilic (TPI) and
 674 hydrophilic (HPI) fraction after 24h and both high and low specific ultraviolet absorbance at 254 nm ($SUVA_{254}$)
 675 values of (a) halo-aldehydes (HAL), column capacity factor k' is not available (NA), low chlorine dose (5 water
 676 samples) (b) haloacetonitriles (HAN), k' is not available (1x 100), low chlorine dose (6 water samples) and (c)
 677 halonitromethanes (HNM), k' is not available (2x 15), low chlorine dose (7 water samples). * = statistical
 678 difference. From the data, it is clear that all families are preferentially formed in the hydrophilic fraction, although
 679 this was not statistically significant for the halonitromethanes

680 This meta-analysis determined the parameters affecting the identification of disinfection by-product
 681 precursors, because no assessments were done so far in the past. This review identified hydrophobic
 682 compounds as having high trihalomethane and haloacetic acid formation potential especially for high
 683 $SUVA_{254}$ and low k' - factor values. Hydrophilic moieties are overall the most important precursors for
 684 the formation of emerging disinfection by-products, but can also not be neglected as trihalomethane
 685 and haloacetic acid precursor when $SUVA_{254}$ of the raw water is low and high column capacity factors
 686 are used. Furthermore, this study could not identify the disinfection by-product precursors based on

687 molecular weight, which might be explained by an unsharp separation of natural organic matter
 688 during membrane fractionation. A graphical summary of all results can be found in Fig. 11.
 689



690
 691 **Fig. 11** Overview scheme of the conclusions drawn in this meta-analysis. NOM = natural organic matter. There is
 692 an indication that ultrafiltration membrane fractionation cannot produce sharply separated fractions. Therefore,
 693 no correlation was found between disinfection by-product formation and molecular weight. During resin
 694 fractionation, chlorination time and dose do not affect the ratio of disinfection by-product formation between the
 695 different fractions, while the specific ultraviolet absorbance at 254 nm (SUVA₂₅₄) and the column capacity factor k'
 696 do have an effect on this ratio.

697 5 Conclusions and Outlook

698 This review critically evaluated different natural organic matter fractionation techniques with regard
699 to disinfection by-product formation. The formation of trihalomethanes, haloacetic acids and
700 emerging disinfection by-products from the different fractions obtained by both membrane and resin
701 fractionation after chlorination was assessed. The general conclusions are:

- 702 • Dead-end, ultrafiltration, membrane fractionation allows the production of fractions in large
703 volumes, but there is an indication that it lacks the ability to perform a sharp separation of
704 the different fractions. Therefore, no relationship was found between molecular weight and
705 disinfection by-product formation potentials.
- 706 • Resin fractionation splits natural organic matter based on polarity. Despite being a generally
707 accepted method of fractionation, the potential of changing the organic matter composition
708 due to the pH changes is often underestimated. The most important observations of this
709 study are:
 - 710 ○ Chlorination time and dose do not influence the proportion of specific disinfection
711 by-product formation potential between different fractions.
 - 712 ○ Hydrophobic compounds are the most important contributors with 10-20 % higher
713 reactivity to both trihalomethane and haloacetic acid formation in waters with high
714 specific ultraviolet absorbance ($SUVA_{254}$), while hydrophobic and hydrophilic
715 compounds are equally important in water with low $SUVA_{254}$. However, hydrophilic
716 compounds have 20-80 % higher reactivity towards emerging disinfection by-
717 products, regardless of $SUVA_{254}$.
 - 718 ○ Increasing the column capacity factor k' *i.e.* the amount of hydrophobic compounds
719 retained on XAD-resins can shift the highest specific formation potential from
720 hydrophobic to hydrophilic fractions.

721 Future research should focus on the development of an alternative membrane fractionation method
722 to have sharply, defined and separated size-based fractions. This allows to clearly mark the effect of
723 a certain physical property to disinfection by-product formation. Furthermore, it is important to
724 report the k' value used in resin fractionation, because it can influence the disinfection by-product
725 formation in the different fractions. In addition, fraction analysis for disinfection by-product
726 formation with chlorine is currently limited to regulated disinfection by-product, with only minor
727 research done in this field for emerging disinfection by-product. These groups of disinfection by-
728 product are formed in lower concentrations, but could exhibit a higher toxicity, and therefore, may
729 cause greater public health problems. Therefore, further research should focus on the formation of a

730 broader group of disinfection by-product in different membrane and resin fractions to increase
731 knowledge on natural organic matter precursors and therefore provide safer drinking water now and
732 in the future.

733 6 Methods

734 6.1 Data collection

735 The Scopus library was used to collect papers from the last 2 decades as a continuation of the review
736 paper of Chow et al. (2005) which was at that time only focused on trihalomethanes. The criteria for
737 selecting a paper were water source (*i.e.* fresh water), disinfectant (*i.e.* chlorine) and the use of
738 preparative fractionation. Natural waters were selected from all over the world, since it is believed
739 that this natural organic matter pool is universal due to the natural processes of synthesis and
740 degradation (Zark and Dittmar, 2018). Since treatment processes can influence the organic matter
741 composition, *e.g.* leakage of soluble microbial products from biological activated carbon, only raw
742 water sources were included (Hong et al., 2018). With all these criteria, 83 papers were selected,
743 resulting in data collection from 396 water samples from all over the world with a high number of
744 publications in the United States and Asia (Fig. S8).

745 6.2 Data processing

746 The data was uniformized to be able to compare all papers with each other. First, the specific
747 disinfection by-product formation potential from each fraction was collected or calculated, if not
748 readily available. This is a normalization parameter defined as the amount of a certain by-product
749 compound or family formed per unit dissolved organic carbon (generally expressed as $\mu\text{g}/\text{mgC}$). In
750 some cases, especially for membrane fractionation, the specific formation potential of different
751 fractions were merged to one single value to obtain a better comparison, *e.g.* < 0.5 kDa and 0.5-
752 1 kDa fraction were merged to < 1 kDa. This was done using the following formula (Kitis et al., 2002):

$$sDBPFP_{new} = \sum_{i=1}^n \left[\frac{m_i}{\sum_{i=1}^n m_i} * sDBPFP_i \right]$$

753 With n the number of fractions to merge in one water sample, m_i the mass of fraction i and $sDBPFP$
754 the specific disinfection by-product formation potential.

755 These values were converted into percentages for each fraction in the following way:

$$\%_i = \frac{sDBPFP_i}{\sum_{i=1}^n sDBPFP_i}$$

756 With n the number of fractions collected from a certain water sample and sDBPFP the specific
757 disinfection by-product formation potential.

758 With this conversion, the relative difference in the specific reaction potential of different fractions
759 towards disinfection by-product formation can be visualized. Therefore, these data were plotted into
760 boxplots to examine the overall relative difference between distinct fractions to a certain disinfection
761 by-product formation deduced from all studied papers. The box itself is ranged within the 1st and 3rd
762 quartile (25th and 75th percentile) with a horizontal line for the 2nd quartile (median). This is also
763 called the interquartile range. The whiskers represent the data that lie within 1.5 times the
764 interquartile range above and below the box. Data exceeding this range were identified as outliers
765 and are represented as dots. The outliers were not removed from the dataset before the statistical
766 analysis.

767 A two-tailed t-test (2 datasets) or a one-way ANOVA (> 2 datasets) were executed when the
768 assumptions for normality and equal variances were valid. The Shapiro-Wilk test was used to see if
769 the data was normally distributed. The F-test (2 datasets) or the Bartlett-test (> 2 datasets) were
770 used to check if all datasets had equal variances. Not-normally distributed data was first transformed
771 in an attempt to make them normally distributed. If these transformations were not successful, non-
772 parametric tests such as the Mann-Whitney U test (2 datasets) or the Kruskal-Wallis test (> 2
773 datasets) were executed. For all tests included, the null hypothesis was rejected when the p-value
774 was smaller than 0.05.

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785 **Ethics approval** not applicable

786 **Consent to participate** not applicable

787 **Consent for publication** not applicable

788 **Availability of data and material** All raw data will be shared through an Open Source repository.

789 **Code availability** not applicable

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