



Title	Presence of the -triketone herbicide tefuryltrione in drinking water sources and its degradation product in drinking waters
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**Presence of the β -Triketone Herbicide Tefuryltrione in Drinking Water
Sources and its Degradation Product in Drinking Waters**

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26 **Abstract**

27 Triketone herbicides are becoming popular because of their herbicidal activity against
28 sulfonylurea-resistant weeds. Among these herbicides, tefuryltrione (TFT) is the first
29 registered herbicide for rice farming, and recently its distribution has grown dramatically.
30 In this study, we developed analytical methods for TFT and its degradation product 2-
31 chloro-4-methylsulfonyl-3-[(tetrahydrofuran-2-yl-methoxy) methyl] benzoic acid
32 (CMTBA). TFT was found frequently in surface waters in rice production areas at
33 concentrations as high as 1.9 µg/L. The maximum observed concentration was lower than
34 but close to 2 µg/L, which is the Japanese reference concentration of ambient water
35 quality for pesticides. However, TFT was not found in any drinking waters even though
36 the source waters were purified by conventional coagulation and filtration processes; this
37 was due to chlorination, which transforms TFT to CMTBA. The conversion rate of TFT
38 to CMBA on chlorination was almost 100%, and CMTBA was stable in the presence of
39 chlorine. Moreover, CMTBA was found in drinking waters sampled from household
40 water taps at a similar concentration to that of TFT in the source water of the water
41 purification plant. Although the acceptable daily intake and the reference concentration
42 of CMTBA are unknown, the highest concentration in drinking water exceeded 0.1 µg/L,
43 which is the maximum allowable concentration for any individual pesticide and its
44 relevant metabolites in the European Union Drinking Directive.

45

46 **Keywords:** pesticide, HPPD inhibitor, river water, chlorination by-products, tap water

47

48

49 **1. Introduction**

50

51 The annual global consumption of pesticides is estimated to be 24 million tons as active
52 ingredients, and these ingredients represent approximately 900 different chemicals
53 (USEPA, 2011). This intentional application of such a huge amount of pesticides to open
54 surface areas may have a strong impact on both the environment and human health. Due
55 to high public concern regarding residual pesticides in drinking water and food,
56 governments restrict authorized concentration in drinking waters through each standard
57 or directive. In drinking water quality standards or directives, however, the degradation
58 products of pesticides are seldom considered. However, some survey studies have
59 reported higher concentrations of degradation products than of original forms in river
60 waters (Hladik et al., 2008; Botta et al., 2009; Iwafune et al., 2010; McMahan et al., 2016).

61 Rice-farming herbicides easily enter natural river waters at higher rates than other
62 pesticides used in upland farming because they are applied to paddy fields where a large
63 amount of water is irrigated, ponded, and drained during the rice-farming seasons (Narita
64 et al., 2014). According to a national survey of drinking and source water quality (Matsui,
65 2016), rice-farming herbicides such as molinate and pretilachlor are detected more
66 frequently at high concentrations than other pesticides. The ADI (acceptable daily intake)
67 values of pesticides, which span a broad range (more than five orders of magnitude),
68 affect the significance of measured concentrations relative to the toxicities of pesticides,
69 because the individual guideline values of pesticides are derived from their ADI values.

70 Given this background information, we focused on a new rice-farming herbicide,
71 tefuryltrione (TFT) (Table 1), and its degradation product. TFT is a β -triketone herbicide,
72 which causes weed whitening and death by inhibiting HPPD (hydroxyphenylpyruvate

73 dioxygenase) activity. Triketone herbicides including TFT are becoming popular,
74 replacing sulfonyleurea herbicides, because of their herbicidal activity against resistant
75 weeds (Itoh et al., 1999; Uchino et al., 2000). In Japan, TFT was registered in 2007, and
76 since then has been increasingly used in rice farming. TFT was also registered in 2015 in
77 Korea (Park et al., 2012), and other triketone herbicides (mesotrione, sulcotrione, and
78 tembotrione) are registered in many other countries, including the USA and several
79 European countries (USEPA, 2007, 2009a; ECHA, 2011). Environmental monitoring
80 information about triketone herbicides is gradually accumulating, as is information about
81 their behaviour during water purification processes (Freitas et al., 2008; Patil et al., 2016;
82 Dumas et al., 2017). However, information is still limited regarding their degradation
83 products (Freitas et al., 2004; Durand et al., 2010; Bensalah et al., 2011; Murati et al.,
84 2012; Jović et al., 2013; Barchanska et al., 2016), in particular those found in drinking
85 water.

86 In an assessment conducted by the Food Safety Commission of Japan (FSC), the ADI of
87 TFT was set at 0.8 $\mu\text{g}/\text{kg}/\text{day}$ (FSC, 2009), and a prospective reference concentration of
88 2 $\mu\text{g}/\text{L}$ can be derived from this ADI value multiplied by standard body weight (50 kg)
89 and allocation factor (10%), divided by drinking water consumption (2 L). This value is
90 the lowest among the herbicides registered in Japan. Yet, TFT is not included in the list
91 of motoring candidates of the Japanese Drinking Water Quality Guideline (JDWQG)
92 (MHLWJ, 2003), and it is not listed in any of the national drinking water quality standards
93 or guidelines. The low ADI value of TFT, coupled with the recent increase in the quantity
94 of TFT that is shipped annually, raises concern that TFT should be monitored in drinking
95 and source waters.

96 Accordingly, the aim of this research was to develop a method to analyse TFT in water,
97 to reveal its presence in drinking and source waters, and to investigate its behaviour
98 during the water purification process. Importantly, we identified a degradation product of

99 TFT during the chlorination process, the presence and behaviour of which are also
100 described.

101

102 **2. Materials and Methods**

103

104 *2.1. Sampling points of river waters*

105 Twelve rivers that flow through Kanagawa prefecture were selected for water sampling.
106 Sampling at the Tsurumi River [Fig. S1 in Supplementary Information (SI)] was
107 conducted first and with the highest frequency of every two weeks from April to
108 September 2013 and then April to September 2014. Sampling at the other rivers was
109 conducted every month from April to July 2014. Because high concentrations were
110 detected in the Shibuta River, sampling was conducted every week from May to June
111 2015. Samples were transported to the laboratory at Kanto Gakuin University for TFT
112 concentration analysis according to the procedure described in the section 2.2. In addition
113 to this sampling and analysis, in 2014 and 2015, sampling and analysis were also
114 conducted in 8 prefectures by waterworks authorities (Fig. S2 and Table S1 in SI).

115

116 *2.2. Analytical method*

117 Because no analytical method for TFT concentration in environmental and drinking
118 waters has yet been reported, we developed one (Fig. S3 in SI) in this study after referring
119 to the analytical method for neonicotinoid pesticides because of their similar low Log-

120 Kow and high water solubility (Kawasaki et al., 2012). After filtrating the sample water
121 through a glass fiber filter with nominal pore size of 1.0 μm (GA-100, Advantec Toyo
122 Kaisha, Ltd.) and adjusting the filtrate to pH 3.0 by adding formic acid (the pH adjustment
123 is less than necessary: it was implemented for the simultaneous analysis of other
124 pesticides), a specified volume (250 mL) of the resultant sample water was passed
125 through an Oasis HLB cartridge (250 mg, Waters Corporation, USA) at a 5 mL/min flow
126 rate by using a concentrator; the Oasis HLB was previously rinsed and conditioned with
127 10 mL of MeOH and 20 mL of ultrapure water (LC/MS analytical grade, Wako Pure
128 Chemical Industries, Ltd., Japan) (Kawasaki et al., 2012). The Oasis HLB was then dried
129 with N_2 gas for 5 minutes, and then it was eluted with 10 mL of MeOH. The volume of
130 the eluate was reduced under an N_2 gas stream to 0.1 mL. After adding 100 μL of a 1%
131 formic acid aqueous solution, that mixture was made up to 1 mL with the ultrapure water
132 and filtrated through a 0.22- μm filter (PTFE, RephiLe Bioscience, Ltd.). The final
133 concentration factor was, therefore, 250 fold. The pretreatment using the Oasis HLB was
134 not carried out with the samples obtained in the laboratory experiment of TFT
135 chlorination because of their high concentrations. Recovery tests for the pretreatment
136 were conducted using distilled water and river water spiked with reagent-grade TFT
137 (Wako Pure Chemical Industries, Ltd. JAPAN) to obtain a concentration of 2 $\mu\text{g/L}$, which
138 is equivalent to the prospective reference concentration in JDWQG. Each test was
139 conducted five times, and the average recovery rate was determined.

140 The liquid chromatography tandem-mass spectrometry (LC-MS/MS) (ACQUITY UPLC
141 System and Quattro Premier XE, Waters Corporation, USA) analytical conditions used
142 are shown in Table S1. The monitor ion and confirmation ion were set to $m/z = 340.8$ and
143 $m/z = 262.0$, respectively. After creating a calibration curve, the detection limit was fixed.
144 The same analytical procedure was applied to the quantification of a degradation product.
145 The monitor and the confirmation ions for the degradation product were set at $m/z = 247.0$

146 and 85.0, respectively. The TFT analyses of the samples taken at the 8 prefectures were
147 conducted at each local waterworks authority according to the above-described method
148 with some modifications. Further details are provided in Table S2 (SI).

149 The quantification limit of TFT was 0.02 $\mu\text{g/L}$ (Table S2). The coefficients of variance
150 (CVs) for multiple analyses ($n = 5$) at 0.02 $\mu\text{g/L}$ were 12.0% and 19.6% for distilled water
151 and the river water, respectively. The recovery ratios, by solid phase extraction and elution,
152 were fairly good; they were 118% ($n = 5$) and 116% ($n = 5$) for distilled water and the
153 river water, respectively, both at 0.02 $\mu\text{g/L}$ TFT (this is 1/100 of the prospective reference
154 concentration of drinking water in Japan, 2 $\mu\text{g/L}$), when the concentration factor was 250
155 fold after extraction and elution.

156

157 *2.3. Identification of the chlorination degradation product of TFT*

158 To detect and identify degradation product(s), we conducted chlorination experiments in
159 glass bottles containing 25 mL of TFT solution. Reagent-grade TFT was added to a
160 phosphate buffer solution of pH 7 to bring the concentration to 0.4 $\mu\text{mol/L}$. Sodium
161 hypochlorite solution was then added to bring the free residual chlorine concentration to
162 1 mg/L as the chlorination reaction proceeded for 2 hours after the addition of the sodium
163 hypochlorite solution. After the chlorination reaction was allowed to proceed for 2 hours,
164 the residual chlorine was quenched to terminate the chlorination reaction by adding 7.5
165 μL of ascorbic acid solution (0.28 mol/L).

166 The chlorination degradation product formed in these chlorination experiments was first
167 analyzed by liquid chromatography time-of-flight mass spectrometry (LC/TOF-MS)
168 (Xevo G2-XS Tof, Waters Corporation). The elemental composition of the degradation

169 product was determined from its accurate mass obtained by LC/TOF-MS analysis. The
170 structural formula of the degradation product was estimated from its elemental
171 composition and the structural formula of the parent compound (TFT) by using a chemical
172 structure estimation software (Elemental Composition, Waters Corporation, USA).

173 The structural formula was further confirmed by using orbitrap–tandem-mass
174 spectrometry (Orbitrap-MS) (Q-Exactive Quadrupole-Orbitrap mass spectrometer
175 equipped with a high-resolution accurate-mass Orbitrap™ detector, Thermo Fisher
176 Scientific, USA). The injection volume was 5 μL and an Acclaim C18 column (150×2.2
177 mm, 2.6 μm) was used in gradient mode with a flow rate of 0.4 μL · min⁻¹. Thirty seconds
178 after the sample injection, the gradient was started at 2% MeOH/98% water (10 mM
179 ammonium acetate solution), and then the ratio linearly increased to reach 98% MeOH at
180 15 min. Ionization was performed in the electrospray positive mode. The flow rates of the
181 auxiliary and sheath gases were 15 (arbitrary units) and 50 (arbitrary units), respectively.
182 A spray voltage of 3 kV and S-less TF level of 50 were applied. The temperature of the
183 ion transfer capillary was 350 °C, and the heart temperature was 250 °C. The resolution
184 of the MS analysis was 70,000. The AGC target was 1×10⁶, and the maximum time of
185 injection was 200 ms. For all samples, a 60–900-amu mass range was applied. For
186 MS/MS analysis, the resolution was set to 17,500, with an isolation window of 5 amu.
187 The collision energy was normalized between 10 and 60%, and the AGC target was 2×10⁵.

188 To confirm the chemical structural formula of the degradation product and to quantify it,
189 a reagent-grade version of the degradation product was obtained from Hayashi Pure
190 Chemical Ind., Ltd. (Osaka, Japan). The analytical method for the degradation product
191 was developed with the LC-MS/MS. After determining the monitor ion and creating a
192 calibration curve, the minimum determination limit was fixed (Table S1). Pretreatment
193 for the extraction and elution using the Oasis HLB cartridge was not conducted because

194 the initial and final concentrations of the samples were sufficiently high without any
195 pretreatment.

196 To observe changes in TFT and the degradation product, a long-term chlorination
197 experiment was conducted. The chlorination condition are the same as that described
198 above except that the chlorination reaction proceeded for 24 hours after the addition of
199 the sodium hypochlorite solution. The analytical condition for the determination of TFT
200 and the degradation product are shown in Table S2 (SI).

201

202 *2.4. Sampling points of tap waters*

203 To determine the level of TFT and the degradation product in drinking water from
204 household water taps, we sampled tap water in Niigata prefecture because TFT sales was
205 high this region compared with others (see the section 3.1). Tap water samples (25 mL)
206 were collected approximately every day from June to August 2015. Immediately after
207 sampling, residual chlorine was removed by adding an ascorbic acid solution of 0.28
208 mol/L at a ratio of 7.5 μ L per 25 mL, and the samples were shipped to the laboratory at
209 Kanto Gakuin University for analysis. Samples were also corrected at the water treatment
210 plant that treats and supplies the drinking water to the household water taps. The source
211 water (37.93124°N, 139.11807°E) and the process water were sampled and analyzed for
212 TFT concentration at the laboratory of the water treatment plant in Niigata prefecture.

213

214 **3. Results and Discussion**

215

216 *3.1. Distribution and use of TFT*

217 TFT is included in 21 commercial pesticide products, all of which are mostly used in rice
218 farming. Of these 21 products, 3 contain TFT as the single active ingredient (FAMIC,
219 2016). The 18 products are multi-component mixtures containing TFT and other active
220 ingredients: 6 products contain oxaziclomefone, 3 contain pyraclonil, 3 contain pyraclonil
221 and metazosulfuron, 3 contain fentrazamide, and 3 contain mefenacet. By examining the
222 TFT contents and the annual sales of these pesticide products, we calculated the total TFT
223 annual sales for each prefecture in Japan (Japan Plant Protection Association, 2010-2015).
224 The quantity of TFT being shipped began to increase in 2009 in Japan, and 44.4 tons were
225 shipped in 2014 (Fig. S4). Yamagata and Niigata prefectures received the largest
226 quantities (Fig. S5). The fact that Kanagawa, the site selected for river water sampling,
227 had high TFT sales relative to the area devoted to rice farming (MAFFJ, 2011) suggests
228 that there was intensive application of TFT in rice farming in this prefecture.

229

230 *3.2. TFT concentrations in river waters and drinking waters*

231 TFT concentrations in the Tsurumi River (the main test river) and the other rivers in
232 Kanagawa prefecture are shown in Fig. 1. The maximum detected concentration was 0.19
233 $\mu\text{g/L}$, and the detection rate was 33% (49 samples out of 146) in 2013. In 2014, the
234 maximum detected concentration increased to 1.14 $\mu\text{g/L}$ and the detection rate was 39%
235 (84 samples out of 213). In 2015, the maximum detected concentration increased further
236 to 1.85 $\mu\text{g/L}$, and the detection rate was 43% (12 samples out of 28). Kanagawa is not a
237 prefecture where a large quantity of TFT was sold, although the TFT quantity divided by
238 the rice-farming field area was moderate among other prefectures (Fig. S5). Therefore,
239 the TFT detection in Kanagawa suggested that contamination with TFT likely also

240 occurred in other prefectures, particularly Niigata and Yamagata, into which a large
241 amount of TFT was shipped, as described in the previous section.

242 Nationwide monitoring of TFT concentrations in rivers, including drinking water sources,
243 was conducted at waterworks authorities in 7 prefectures, including Niigata in 2014 and
244 2015. The results are shown in Fig. 2. TFT was detected in all of the river waters of the
245 prefectures tested. In Niigata and Fukuoka, the river waters used as source waters for
246 drinking water production exhibited the maximum TFT concentration of 0.81 $\mu\text{g/L}$. From
247 the end of May to the middle of June both 2014 and 2015, the primary period when TFT
248 was applied to rice fields, the concentrations were higher. The high concentrations were
249 observed in small rivers whose catchment areas were used mainly for rice farming. The
250 maximum observed concentration was 1.9 $\mu\text{g/L}$, which was near 2 $\mu\text{g/L}$: the prospective
251 reference concentration of the DWQG and the predicted environmental concentration of
252 environmental risk assessment for ambient water (MOEJ, 2009).

253 However, TFT was not detected in any of the finished waters in the water treatment plants
254 of the water authorities (Table S4), indicating that TFT might have been removed or
255 transformed during the water treatment processes. Some water treatment plants use
256 conventional water treatment processes such as coagulation, sedimentation, filtration, and
257 chlorination. It was unlikely for the TFT to be removed by coagulation, sedimentation, or
258 filtration because its water solubility (64.2 g/L at pH 7) is high and its Log-Kow (1.05) is
259 relatively low. In fact, we observed no TFT removal by coagulation and membrane
260 filtration in our laboratory experiments (Fig. S6). In the water purification plants, TFT
261 was still detectable in the process water after coagulation-sedimentation at the same level
262 as that in the influent water (Fig. S7). However, TFT disappeared after sand filtration and
263 chlorination. It is highly probable that the TFT reacted with the chlorine and degraded.
264 We therefore hypothesized that degradation products were formed from the TFT during
265 chlorination rather than the TFT being completely mineralized.

267 *3.3. Identification and quantification of a chlorination degradation product of TFT*

268 Orbitrap-MS chromatograms were obtained in the positive mode before and after
269 chlorination of the TFT-containing solution (Fig. 3). No peak corresponding to TFT was
270 observed for the sample after chlorination, but a single peak was observed, suggesting the
271 production of a main degradation product. The MS spectra for the peak showed a
272 molecular ion at 349.052, which indicated a compound consisting of C₁₄H₁₇ClO₆S. From
273 these data, we estimated the structure and proposed that the main product was probably
274 2-chloro-4-methylsulfonyl-3-[(tetrahydrofuran-2-yl-methoxy) methyl] benzoic acid
275 (CMTBA).

276 The MS and MS/MS characteristics, including the theoretical and observed *m/z* values
277 and the molecular structure, are shown in Table 1. The chemical structure of CMTBA was
278 in agreement with the molecular formula obtained from the exact mass of the molecular
279 ion. The MS spectra of CMTBA showed an NH₄-adapted molecular ion at 366 Da and a
280 protonated molecular ion at 349 Da. For this product, an isotopic distribution typical of
281 the presence of one chlorine atom was observed. A mass loss of 94 was observed for
282 CMTBA to the mass of its parent TFT. Moreover, no carboxylic acid function loss was
283 observed in the MS/MS analyses. Therefore, CMTBA would be formed by the cleavage
284 of the ether bond of the chemical side chain of TFT. The formation of CMTBA was finally
285 confirmed by observing that the ratio of the two major fragments for the chlorinated TFT
286 solution was the same as that for a reagent-grade version of CMTBA.

287 Quantification of the TFT and CMTBA concentrations before and after chlorination are
288 shown in Fig. 4. The CMTBA concentration after chlorination was almost the same as the
289 TFT concentration before chlorination. TFT was not detected after chlorination.

290 Therefore, TFT was entirely transformed to CMTBA: the transformation percentage of
291 TFT to CMTBA was 94–103%. When a solution containing only CMTBA was subjected
292 to chlorination, the CMTBA concentration did not change, even after 24 hours. These
293 data indicate that CMTBA, formed by chlorination, is stable in the presence of chlorine,
294 and no further degradation of CMTBA occurs. According to the agrochemical evaluation
295 report (FSC, 2009), CMTBA is a degradation product in plant fate tests, soil fate tests,
296 and aquatic photo-degradation tests. However, in these tests the transformation
297 percentage of TFT to CMTBA was very low (less than 10%) (FSC, 2009). Therefore, any
298 special reaction condition in the presence of chlorine would transform TFT to its stable
299 degradation product CMTBA. The almost 100% transformation percentage of TFT to
300 CMTBA and the stability of CMTBA in the presence of chlorine suggest that CMTBA
301 may be present in drinking water from household water taps if the water undergoes
302 chlorination at the water treatment facility.

303

304 *3.5. Presence of CMTBA in drinking water and its source water*

305 TFT and its degradation product CMTBA were measured in tap waters in Niigata
306 prefecture (Fig. 5). Niigata was selected because of the large amount of TFT purchased
307 and the high level of TFT detection in the river water (the source water of the drinking
308 water). TFT was not detected in any of the tap water samples, but CMTBA was detected
309 from late May to the middle of July 2015. The highest observed concentration was 0.35
310 $\mu\text{g/L}$. Although this was low compared with the TFT reference concentration of Japan (2
311 $\mu\text{g/L}$), it exceeded the 0.1 $\mu\text{g/L}$ of European Union (EU) Drinking Water Directive
312 (European Union, 1998). Of the 50 samples tested, 36 (72%) contained CMTBA at
313 concentrations $> 0.1 \mu\text{g/L}$. TFT concentrations in the source waters of the water
314 purification plant of Niigata showed a similar trend to that of CMTBA concentrations in

315 tap waters. CMTBA concentrations in tap waters were sometimes higher than TFT
316 concentrations in the source waters, but this could have been due 1) to the presence of
317 CMTBA in the source waters, 2) to the limited number of samplings and analyses
318 conducted for raw water at the water purification plant, and/or 3) to a time lag in water
319 distribution from purification at the plant to retrieval from the household water tap.

320

321 *3.6. Implications*

322 In drinking water quality guidelines and standards, active ingredients of pesticides are
323 usually listed, but their degradation products are seldom considered (WHO, 2011)
324 (USEPA, 2009b). The EU directive refers to degradation compounds, but the compounds
325 are not specifically named (European Union, 1998). Oxon, sulfone, and sulfoxide, which
326 are by-products formed from organophosphorus pesticides, are listed in the JDWQG
327 (MHLWJ, 2003). These products are formed by chlorination process for the water
328 purification as well as environmental processes, and they are generally no less toxic than
329 their parent compounds (Chambers and Carr, 1993). Their concentrations in drinking
330 waters are monitored by water authorities, and the detection of these degradation products
331 is reported in the Water Supply Statistics (JWWA, 2009–2012). In this context, our data
332 clearly call for attention to be paid to the degradation product (CMTBA) of TFT.
333 Moreover, our findings highlight the need to also consider the degradation products of
334 the other triketone herbicides. Actually, the degradation of other triketone herbicides
335 follows the same pattern as TFT (Dumas et al., 2017).

336 The results of acute toxicity tests in rats indicate that the acute toxicities are low ($LD_{50} >$
337 2500 (mg/kg) for TFT and > 2500 (mg/kg) for CMTBA) (FSC, 2009). By using the EPI
338 Suite (USEPA, 2012), we compared CMTBA and TFT for their acute toxicity against

339 aquatic organisms, and we found that CMTBA has less toxic than TFT: in fish, the 96-h
340 LD₅₀ for TFT was 31 mg/L, whereas that for CMTBA was 20.4 g/L, and in daphnia, the
341 48-h LD₅₀ for TFT was 102 mg/L, whereas that for CMTBA was 10.6 g/L. No
342 mutagenicity would be seen for CMTBA according to a reverse mutation test with *S.*
343 *typhimurium* (TA98, TA100, TA1535, TA1537) with and without S9 mix (FSC, 2009).
344 The ADI for TFT was derived from a two-year chronic toxicity test with rats that
345 confirmed that corneal opacity and keratitis could occur at the lowest dose (FSC, 2009).
346 The mechanism behind this corneal effect in rats is HPPD inhibition: triketone-based
347 compounds inhibit HPPD in the liver, increasing the blood tyrosine concentration, and
348 uptake of tyrosine crystals by corneal epithelial cells (FSC, 2009). In plants, TFT inhibits
349 HPPD, thereby blocking the formation of homoetisate, which leads to foliage bleaching.
350 In an *in vitro* study using the HPPD of *arabidopsis thaliana*, a popular model plant, the
351 inhibitory activity was lower for CMTBA than for TFT(MHLWJ, 2016) . In mammals,
352 therefore, the inhibitory activity of CMTBA may be similarly lower than that of TFT,
353 because the basic structure of triketone is degraded in CMTBA. Mesotrione, which is
354 another triketone herbicide, forms two major degradation products [MNBA (2-
355 methylsulfonyl-4-nitrobenzoic acid) and AMBA (2-amino-4-methanesulfonyl benzoic
356 acid)] (FSC, 2009), possibly through reaction similar to the degradation of TFT. In an *in*
357 *vitro* test, MNBA weakly inhibits HPPD, but the inhibitory activity is lower than the
358 parent, mesotrione (FSC, 2009). AMBA might be less toxic because it is more degraded.
359 Compared with TFT, overall, CMTBA is considered to have no higher chronic toxicity
360 through the HPPD inhibition, which facilitates the establishment of the ADI of TFT.
361 However, given the high concentrations of CMTBA found in drinking waters, further
362 study of its toxicity might be needed to confirm that CMTBA is indeed lower in the
363 chronic toxicity than TFT.

364

365

366 **4. Conclusion**

367 1) An intensive survey investigating rivers in Kanagawa prefecture revealed TFT
368 contamination. TFT was detected in 37% of 387 samples analysed; concentrations ranged
369 from 0.02 to 1.85 $\mu\text{g/L}$. In subsequent examinations of river waters used as drinking water
370 sources in other prefectures with high rice-farming activity, TFT was detected at
371 concentrations up to 0.81 $\mu\text{g/L}$ during the period when TFT was applied to the rice-
372 farming paddy.

373 2) TFT was not removed by coagulation, but it was 100% transformed by chlorination to
374 CMTBA. CMTBA was stable in the presence of chlorine.

375 3) CMTBA was found in drinking water sampled from a household water tap. The
376 concentrations of CMTBA in drinking waters were similar to those of TFT in the source
377 waters of the drinking waters. The highest observed concentration was 0.35 $\mu\text{g/L}$. The
378 reference concentration of CMTBA was not derived because there is no defined ADI
379 value for CMTBA, but the concentration of CMTBA exceeded 0.1 $\mu\text{g/L}$, the maximum
380 allowable concentration according to the EU directive.

381

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392 no official endorsement should be inferred.

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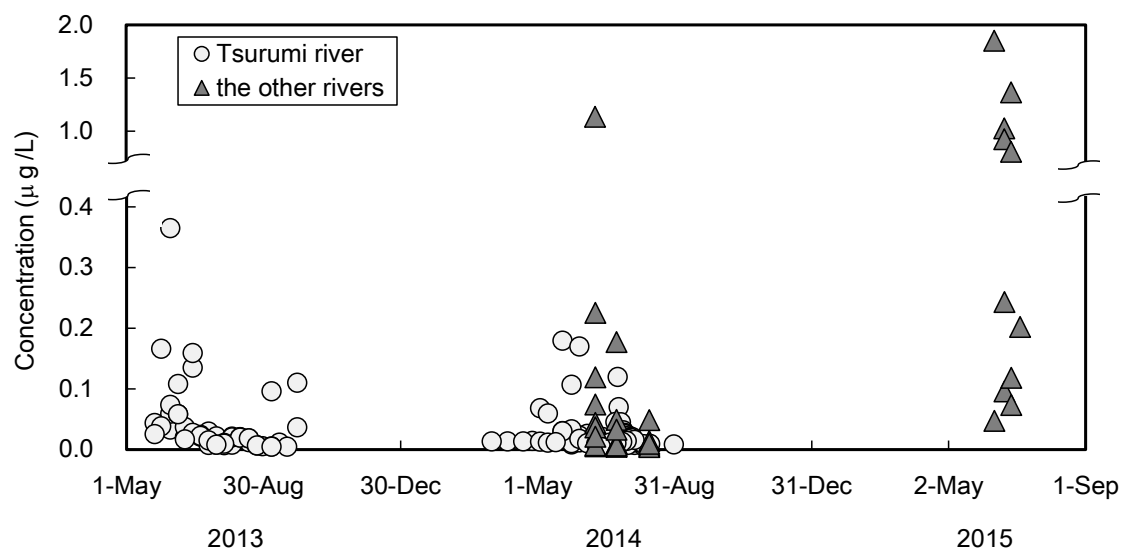
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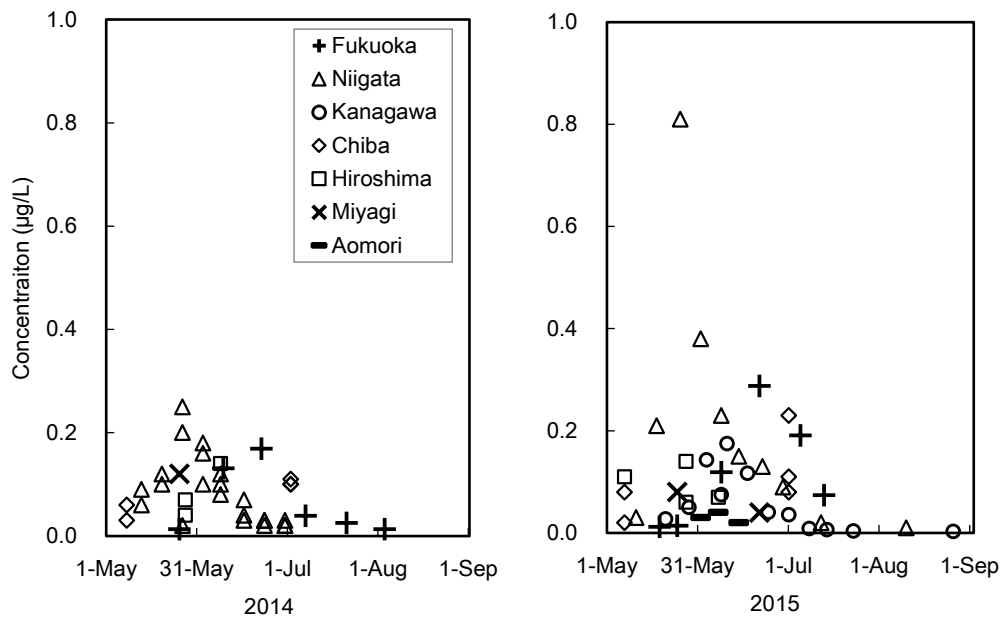
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Fig. 1. Changes in TFT concentrations in the Tsurumi River and other rivers, including the Shibuta and Suzu Rivers, in Kanagawa Prefecture.



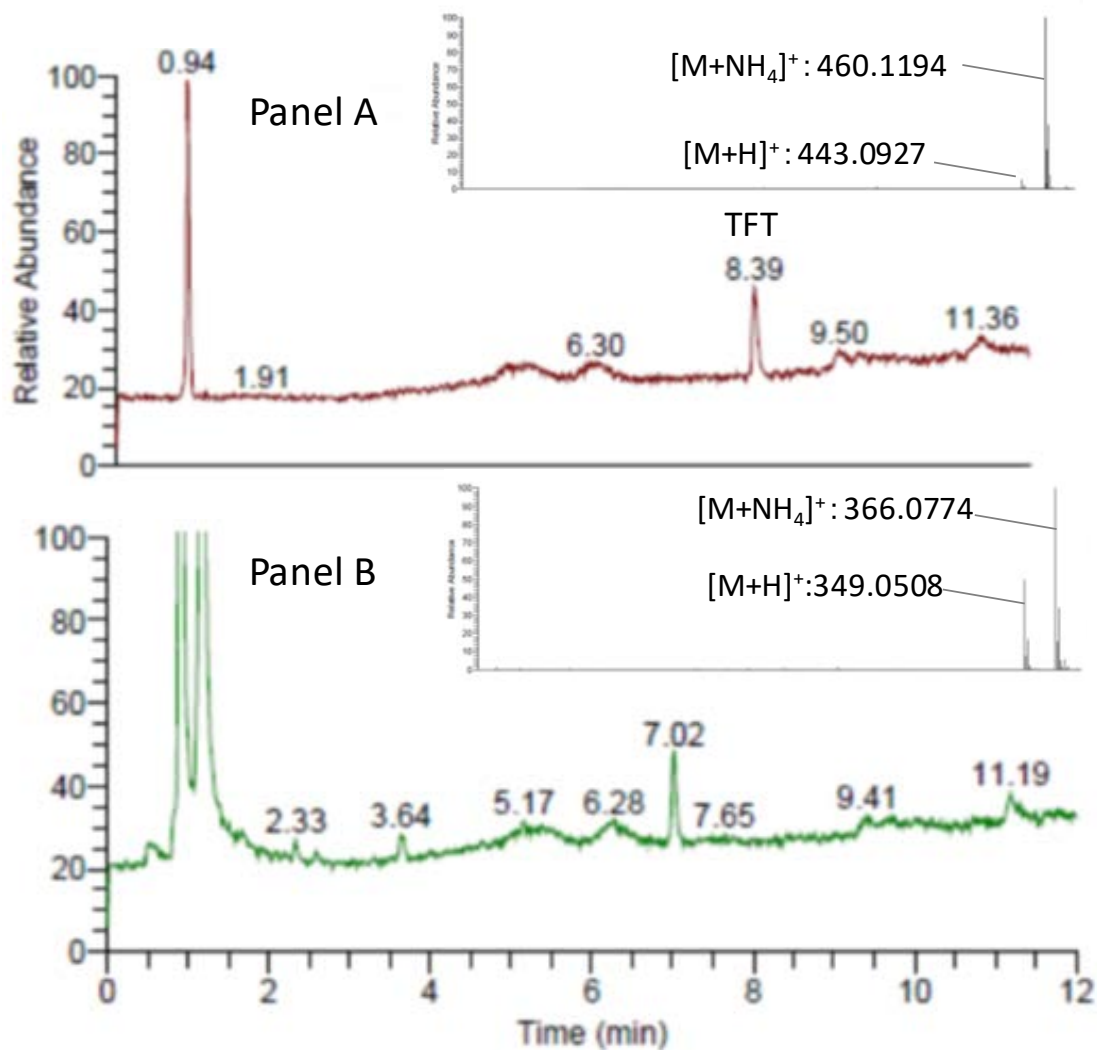
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13 Fig. 2. Changes in TFT concentrations in river waters used as source waters for drinking
 14 waters.

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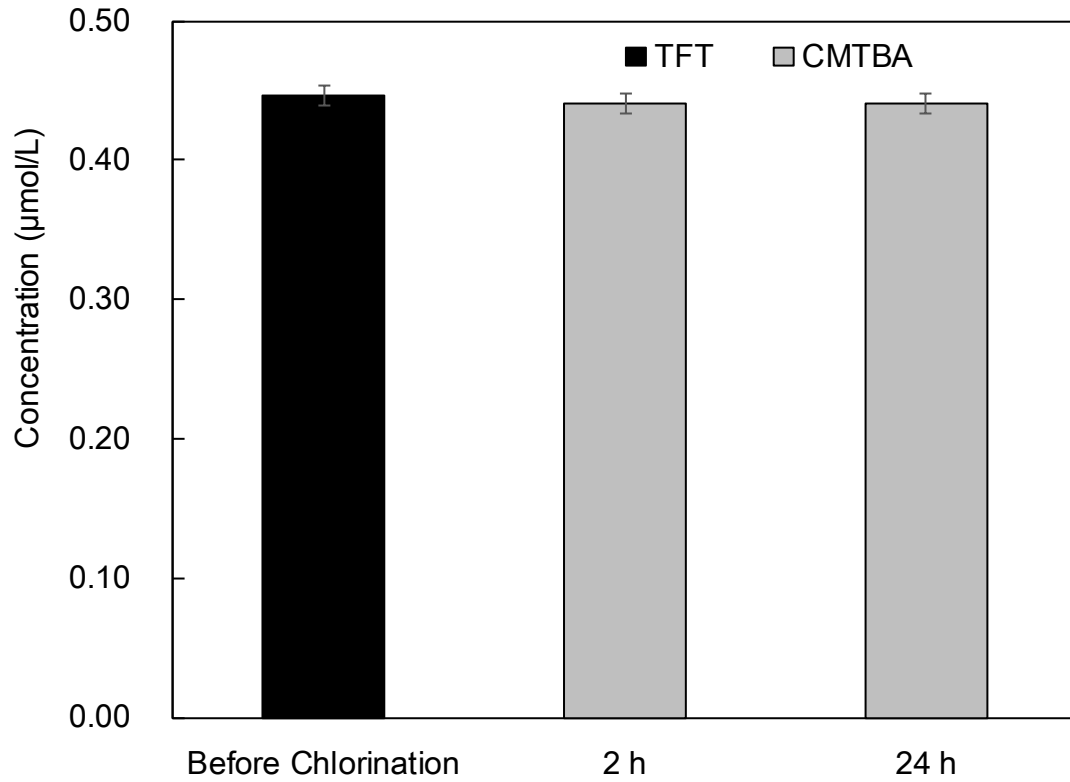
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19 Fig. 3. Orbitrap-MS chromatographs of samples obtained (Panel A) before and (Panel B)
 20 after chlorination of a TFT-containing solution. The small panels in Panels A and
 21 B are the MS spectra corresponding to the chromatogram peaks at 8.39 min (TFT)
 22 and 7.02 min (CMTBA), respectively.



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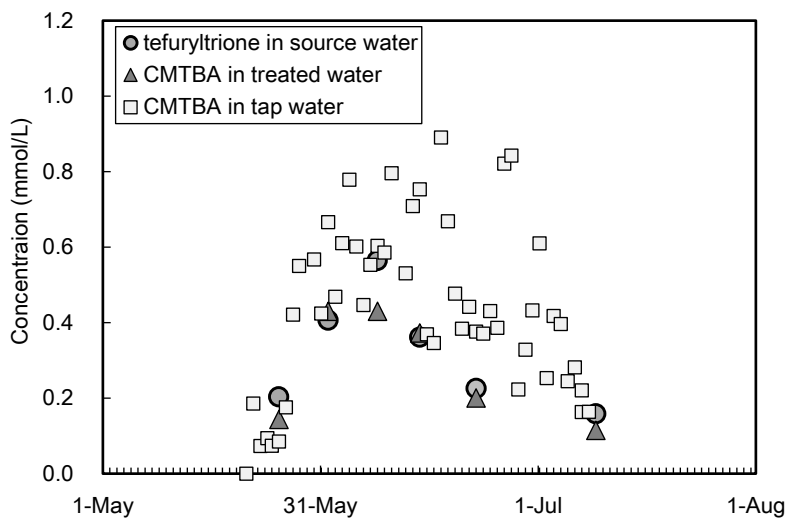
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25 Fig. 4. Changes in TFT and CMTBA concentrations due to chlorination (the error bars
 26 show SD for triplicate samples).

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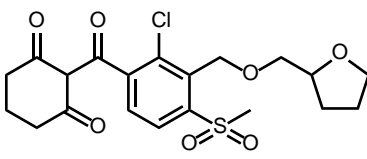
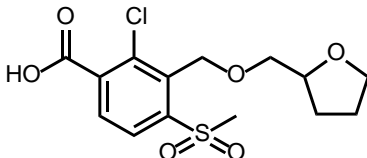
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32 Fig. 6. Changes in TFT and CMTBA concentrations in water sampled from household tap
33 water, source water of drinking water, and treated water at the water purification
34 plant.

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36 Table 1. Mass spectrum characteristics of TFT and its degradation product (CMTBA).

	Composition	Theoretical m/z [M-NH ₄] ⁺	Observed m/z [M-NH ₄] ⁺	Δ ppm	MS	MS2	Structure
TFT	C ₂₀ H ₂₇ O ₇ NCIS	460.1191	460.1194	0.593	460.1194	262.0392 85.0648 305.0479 341.0242	
CMTBA	C ₁₄ H ₂₁ O ₆ NCIS	366.0773	366.0772	-0.17	366.0774	349.0507 85.0647 246.9823	

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2 **Supplementary Information**

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5 **Frequent Presence of the β -Triketone Herbicide Tefuryltrione in Drinking**
6 **Water Sources and its Degradation Product in Drinking Waters**

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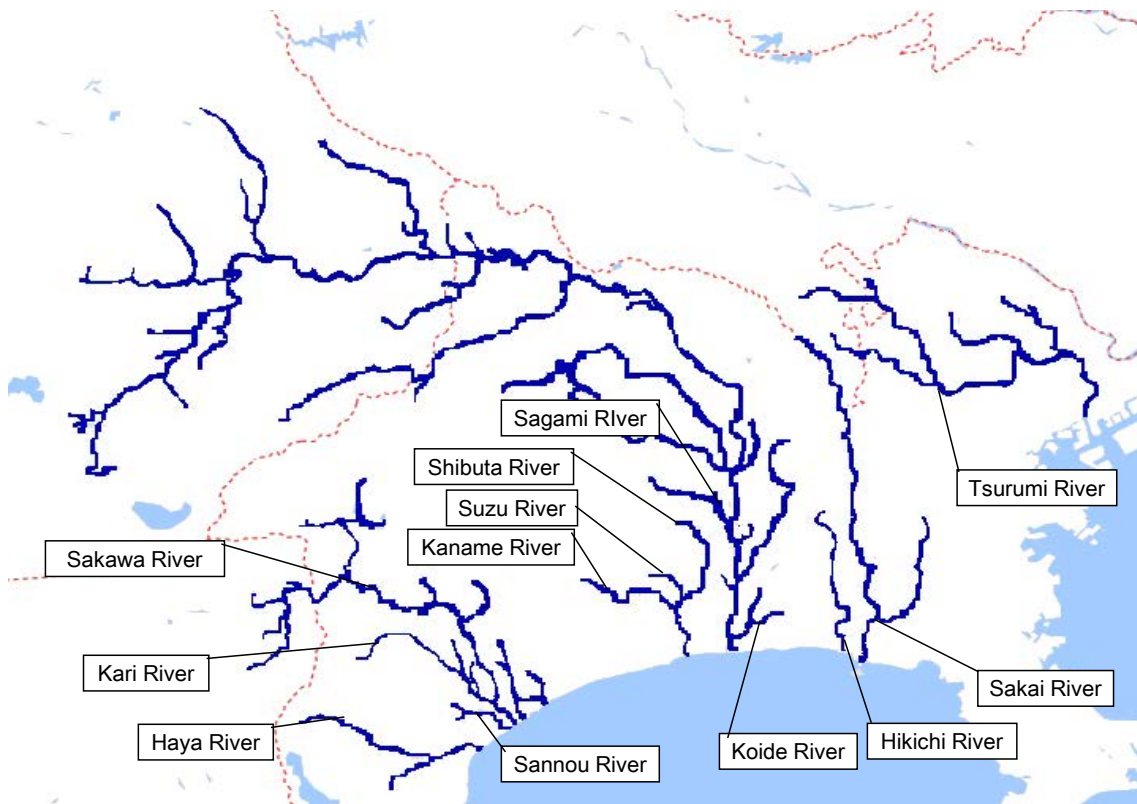
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32 Fig. S1. Sampling points in Kanagawa Prefecture, Japan (the blue lines are rivers, and
33 the dashed red lines show the prefecture border).

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40 Fig. S2. Prefectures investigated in this research (the dashed red lines show the prefecture
41 borders).

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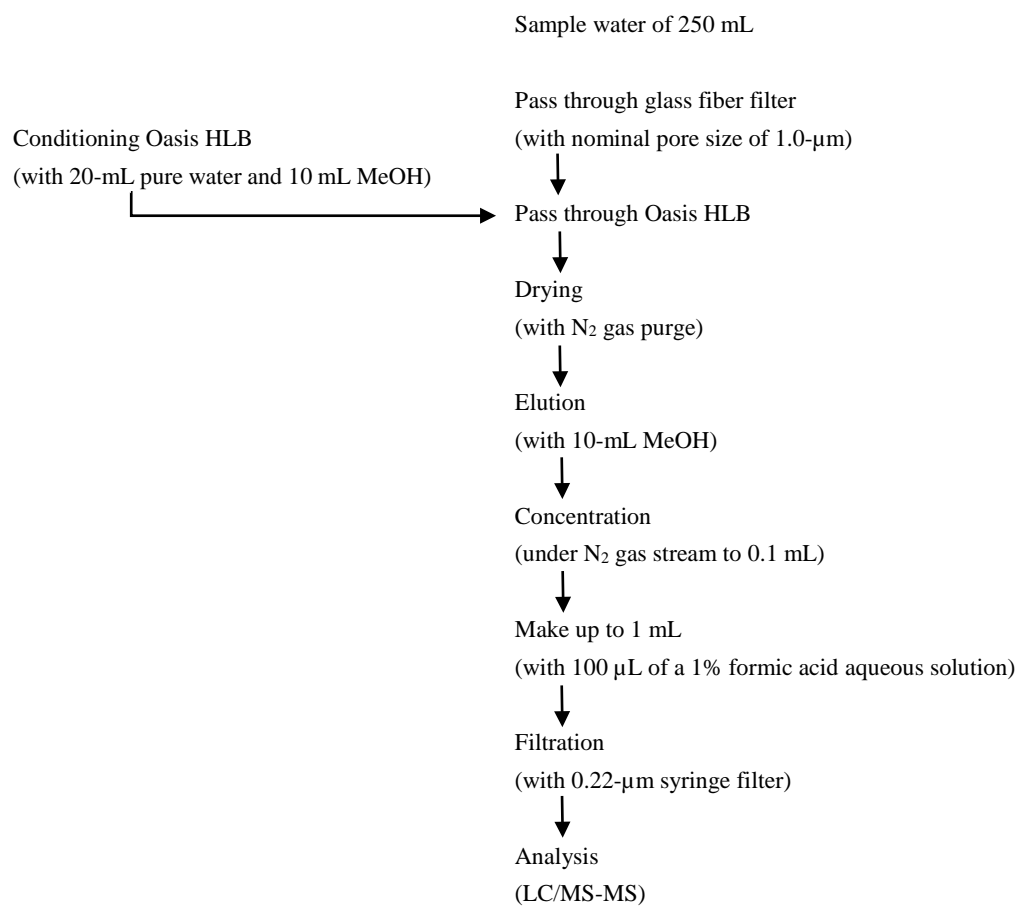


Fig. S3. Pretreatment flow for LC-MS/MS analysis.

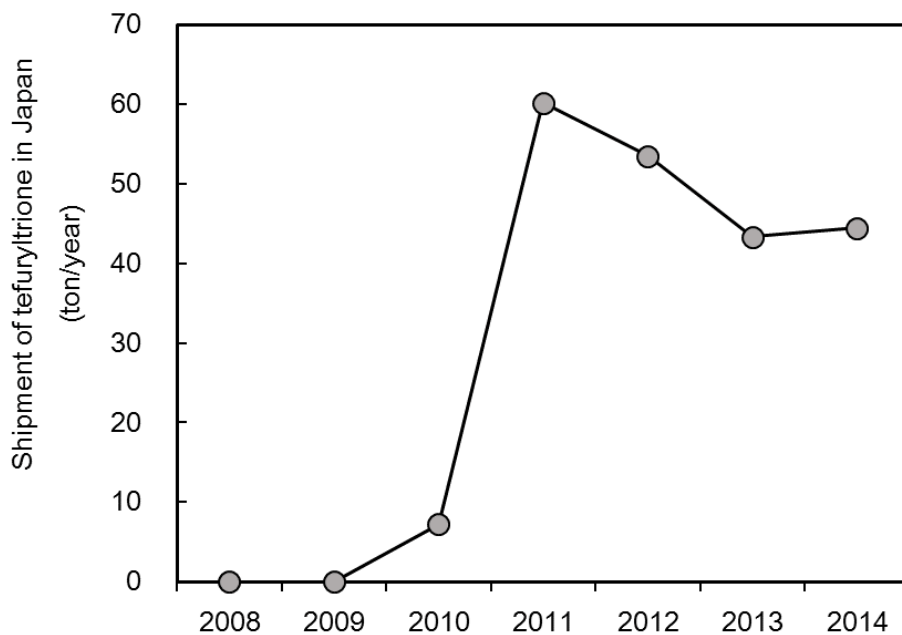


Fig. S4. TFT shipping in Japan.

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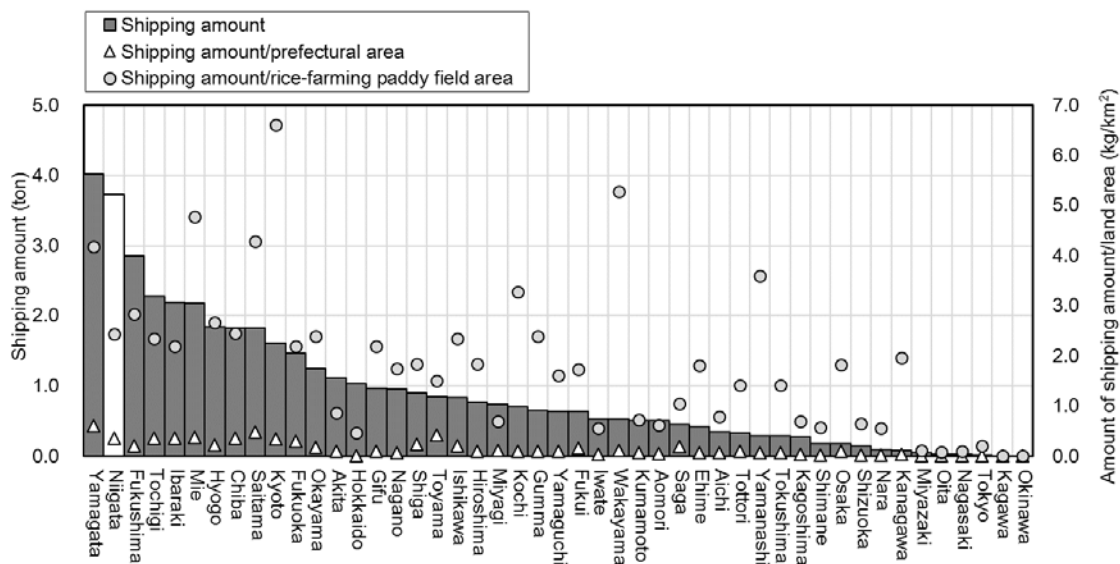
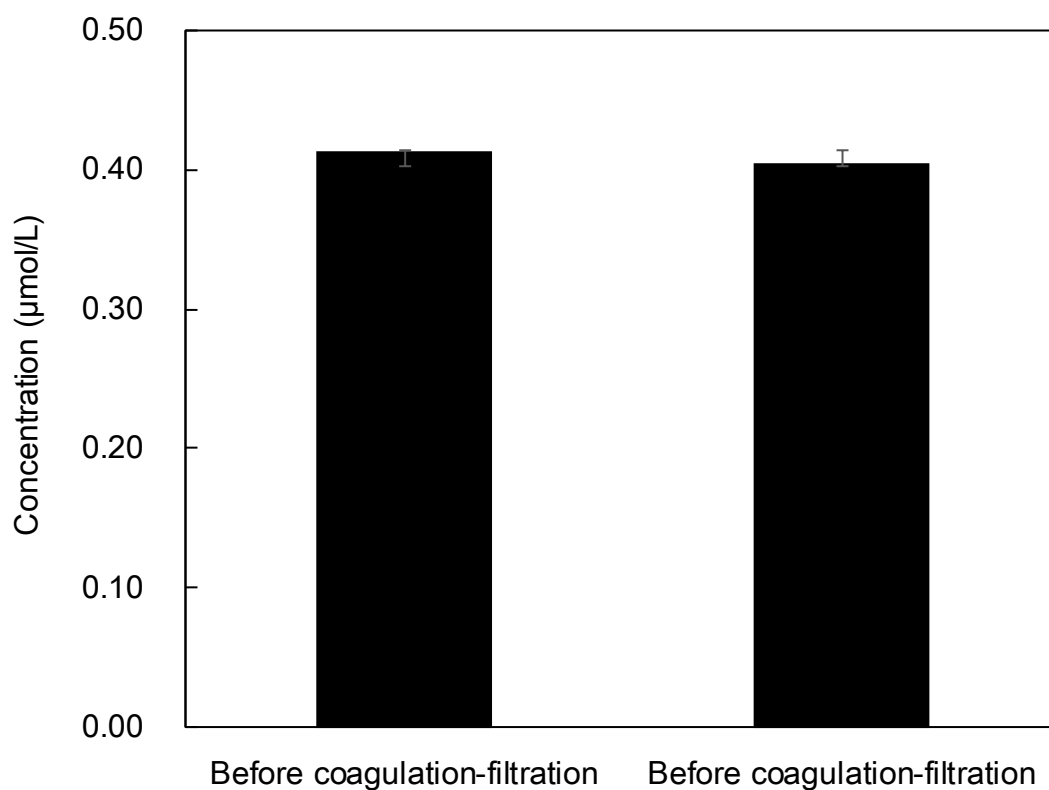


Fig. S5. Total TFT sales, TFT sales per land area, and TFT sales per rice-field area for each prefecture.

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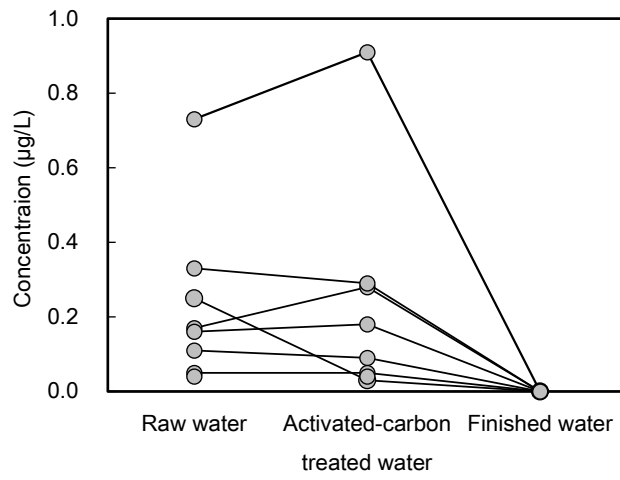
65 Fig. S6. Changes in TFT concentration after coagulation, settling and membrane filtration.
66 Coagulant (poly-aluminum chloride) dose: 20 mg-Al/L. Rapid mixing: 150 rpm.
67 Slow mixing: 40 rpm. Settling: 10 min, Pore size of membrane filter: 0.22 µm.
68 pH: 6.5. Temperature: 20 °C. Analytical condition of TFT: Table 1S. The error
69 bars show SD for triplicate samples.

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75 Fig. S7. Changes in TFT concentration during water treatment processes (May to June,
 76 2015, the Waterworks Bureau of the City of Niigata).

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78 Table S1. Analytical methods applied at Kanto Gakuin University and at the water
79 supply facilities in the 8 prefectures.

	Laboratory of Kanto Gakuin University (river and tap water samples)	Laboratory of Kanto Gakuin University (coagulation and chlorination experiments)	Nigata	Kanagawa	Aomori	Hiroshima	Miyagi	Fukuoka	Chiba
Pretreatment	SPE: Oasis HLB (Waters)	Filtration	SPE: Oasis HLB (Waters)	SPE:Sep-Pak PS-2 and Oasis HLB (Waters)	Filtration	Filtration	Filtration	SPE:Sep-Pak PS2 (waters)	Filtration
LC	AQUITY UPLC (Waters)	UltiMate3000 (Thermo Fisher Scientific)	Quattro Micro API (Waters)	Acquity UPLC (Waters)	AQUITY UPLC (Waters)	NexeraX2 (Shimadzu)	6410B (Agilent)	UltiMate3000 (Thermo Fisher Scientific)	AQUITY UPLC (Waters)
Column	ACQUITY UPLC HSS T3, 2.1 × 100 mm, 1.8 μm (Waters)	Acclaim RSLC C18, 2.1 × 100 mm, 2.2 μm (Thermo Fisher Scientific)	Atlantis dC18, 2.1 × 150 mm, 3 μm (Waters)	ACQUITY UPLC HSS T3, 2.1 × 100 mm, 1.8 μm (Waters)	ACQUITY UPLC HSS T3, 2.1 × 100 mm, 1.8 μm (Waters)	L-column2 ODS, 2.1 × 75 mm, 2 μm (CERI)	ACQUITY UPLC HSS T3, 2.1 × 100 mm, 1.8 μm (Waters)	Mightysil RP-18 PA, 2.0 × 100 mm, 3 μm (Kanto Chemical)	ACQUITY UPLC HSS T3, 2.1 × 100 mm, 1.8 μm (Waters)
Gradient condition	A: 90 % → (14.0 min) → 5 % → (2.5 min) → 5 % → (0.1 min) → 90 % →(3.4 min))	A: 98 % → (1.5 min) → 60 % → (1.5 min) → 40 % → (1 min) → 2 % →(1.0 min) → 98 % → (0.5 min)	A: 90 % → (2.0 min) → 55 % → (15.0 min) → 0 % → (20.0 min) → 90 %, C: 1 %	A: 100 % → (5.0 min) → 50 % → (3.0 min) → 5 %	A: 99 % → (0.5 min) → 60 % → (4.0 min) → 25 % → (8.0 min) → 1 % → (10.0 min) →99 %	A: 1 % → (9.8 min) → 98% → (7.7 min) → 98 % → (0.1 min) → 1 % → (7.5 min) →1 %	A: 80% → (1.0 min) → 60 % → (9.5 min) → 5%	A: 99 % → (1.0 min) → 99 % → (3.0 min) → 40 % → (7.0 min) → 10 % → (8.5 min) → 10 % → (8.51 min) → 2 % → (9.5 min) → 2 % → (9.51 min) → 99 % → (15.0 min) → 99 %	A: 98 % → (1.5 min) → 30 % → (1.5 min) → 5 % → (3.5 min) → 5 % →(7.0 min) → 98 % → (5.0 min)
Mobile phase	A: 0.05% formic acid in 2 mM ammonium acetate, B: MeOH in 2 mM ammonium acetate A: 0.05% formic acid in 2 mM ammonium acetate, B: MeOH in 2 mM ammonium acetate	A:10 mM ammonium acetate, B:MeOH	A:Water, B:MeOH, C:1 % formic acid	A: 0.2 % Formic acid : Acetonitrile = 95:5, B: Acetonitrile	A: 0.05 % formic acid, B:MeOH	A: 0.05% formic acid + 0.1% acetate acid, B:MeOH	A:5 mM ammonium acetate, B:MeOH	A:0.1 % formic acid, B:0.1 % formic acid MeOH	A: 0.05 % formic acid, B:MeOH
Injection volume	5 μL	5 μL	50 μL	5 μL	30 μL	30 μL	30 μL	2 μL	40 μL
Flow rate	0. mL min ⁻¹	0.3 mL min ⁻¹	0.2 mL min ⁻¹	0.35 mL min ⁻¹	0.4 mL min ⁻¹	0.2 mL min ⁻¹	0.3 mL min ⁻¹	0.3 mL min ⁻¹	0.4 mL min ⁻¹
Column temperature	40 °C	40 °C	40 °C	45 °C	40 °C	40 °C	40 °C	40 °C	40 °C
MS	Xevo TQ-S (Waters)	Q-Exactive Focus (Thermo Fisher Scientific)	Quattro micro API (Waters)	Xevo TQ MS (Waters)	Xevo TQ-S (Waters)	LC-8040 (Shimadzu)	1200SL(Agilent)	TSQ Quantiva (Thermo Fisher Scientific)	Xevo TQ MS (Waters)
Ionization	ESI positive	ESI positive	ESI positive	ESI positive	ESI positive	ESI positive	ESI Positive	ESI Positive	ESI positive
m/z	443.10, 341.05	460.1194, 366.0774	443.10, 261.9	443.10, 341.05	443.05, 341.03	443.10, 341.05	460.2, 341.1	459.9, 443	443.10, 261.9

Detection Limit (µg/L)	0.0004	0.01	0.01	0.002	0.02	0.04	0.02	0.01	0.02
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83 Table S2. TFT and CMTBA recovery rates and CVs.

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Target	Water	Recover rate (%)	CV (%)	n	Concentration (µg/L)	Concentration method
TFT	Distillated water	116	12.0	5	0.02	solid-phase extraction
	River water	118	19.6	5	0.02	solid-phase extraction

Target	Water	Recover rate (%)	CV (%)	n	Concentration (µg/L)	Concentration method
CMTBA	Distillated water	97	9	5	0.1	No concentration

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88 Table S3. Detection of TFT in source waters and finished waters at water treatment plants.

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Site of water treatment plant	Source water		Finished water	
	Number of samples	Number of detected samples	Number of samples	Number of detected samples
Kanagawa	43	1	43	0
Miyagi	8	1	8	0
Chiba	8	3	24	0
Niigata	51	22	85	0
Hiroshima	25	3	25	0
Fukuoka	14	14	14	0

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