

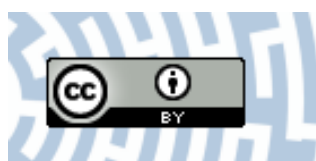


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# Transformation and ecotoxicological effects of iodinated X-ray contrast media

Agnieszka Nowak · Gabriela Pacek · Agnieszka Mrozik

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**Abstract** Iodinated X-ray contrast media (ICM) such as diatrizoate, iohexol, iomeprol, iopamidol, and iopromide are commonly used in medical imaging for radiological visualization of a variety of anatomic structures. Because of their highly persistent nature and poor removal by conventional wastewater treatment, ICM can often remain unchanged after entering the environment or they are transformed into many different by-products in complex physical, chemical, and biological processes. Large amounts of ICM and their by-products are found in natural waters, groundwater, drinking water (up to 100 µg/L), and even in soil, where they can be a potential threat to the inhabitants of these environments. Because knowledge about the fate of ICM in various environments is dispersed and it concerns specific areas, the main purpose of this review is to summarize the available information about their occurrence, chemical and biological transformation/degradation, and toxicity to living organisms. The topics discussed particularly focus on mechanisms of ICM degradation/transformation in water using advanced oxidation processes and the biotransformation/biodegradation of ICM by microorganisms under different conditions, as well as the toxicity of ICM and their transformation by-

products to humans and other organisms. Although environmental risk is not expected from the parent compounds of ICM, their continuous input to the water and the formation of toxic by-products may constitute a long-term potential risk for living organisms. Therefore, monitoring the transport and fate of ICM in various environments seems necessary.

**Keywords** Iodinated contrast media · Transformation/biotransformation products · Advanced oxidation processes · Iodinated disinfection by-products · Toxicity

## 1 Introduction

Constantly increasing global consumption of medicines by humans contributes to the systematic release of these compounds into the environment. It was reported that more than 600 pharmaceutical substances are present in aquatic environments at concentrations up to 10 µg/L (Küster and Adler 2014). As many researchers have reported, some of these compounds cause undesirable effects in living organisms (Huerta et al. 2012; Deo and Halden 2013; aus der Beek et al. 2016). For this reason, in 2013, the European Parliament and the Council of the European Union placed pharmaceuticals such as diclofenac, 17-β-estradiol, 17-α-ethinylestradiol and macrolide antibiotics:

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**Table 1** Recommended doses and physicochemical properties of selected ICM (pubchem.ncbi.nlm.nih.gov and drugbank.ca)

Doses/properties	Diatrizoate	Iomeprol	Iopromide	Iohexol	Iopamidol
Dose, g	0.236–118 (Bayer Inc.)	0.11–139 (Bracco UK Ltd)	2.0–158 (Bayer Inc.)	2.5–130 (GE Healthcare Inc.)	7.5–170 (Bracco UK Ltd.)
Molecular mass, g/mol	613.916	777.089	791.116	821.142	777.089
Log P	3.30	– 1.80	– 2.05	– 3.05	– 2.42
Solubility, mg/mL	0.107	0.155	0.092	0.796	0.117
Melting point, °C	261–262	198–203	145–149	174–180	300
Charge	Ionic	Non-ionic	Non-ionic	Non-ionic	Non-ionic
Osmolality	High	Low	Low	Low	Low
Topological polar surface area, Å <sup>2</sup>	95.5	180	169	200	188
Polarizability, Å <sup>2</sup>	38.43	55.19	57.65	60.37	55.67
pKa (strongest acid)	2.17	5.65	4.23	11.73	4.15
pKa (strongest base)	– 4.2	2.53	2.19	– 3	1.42

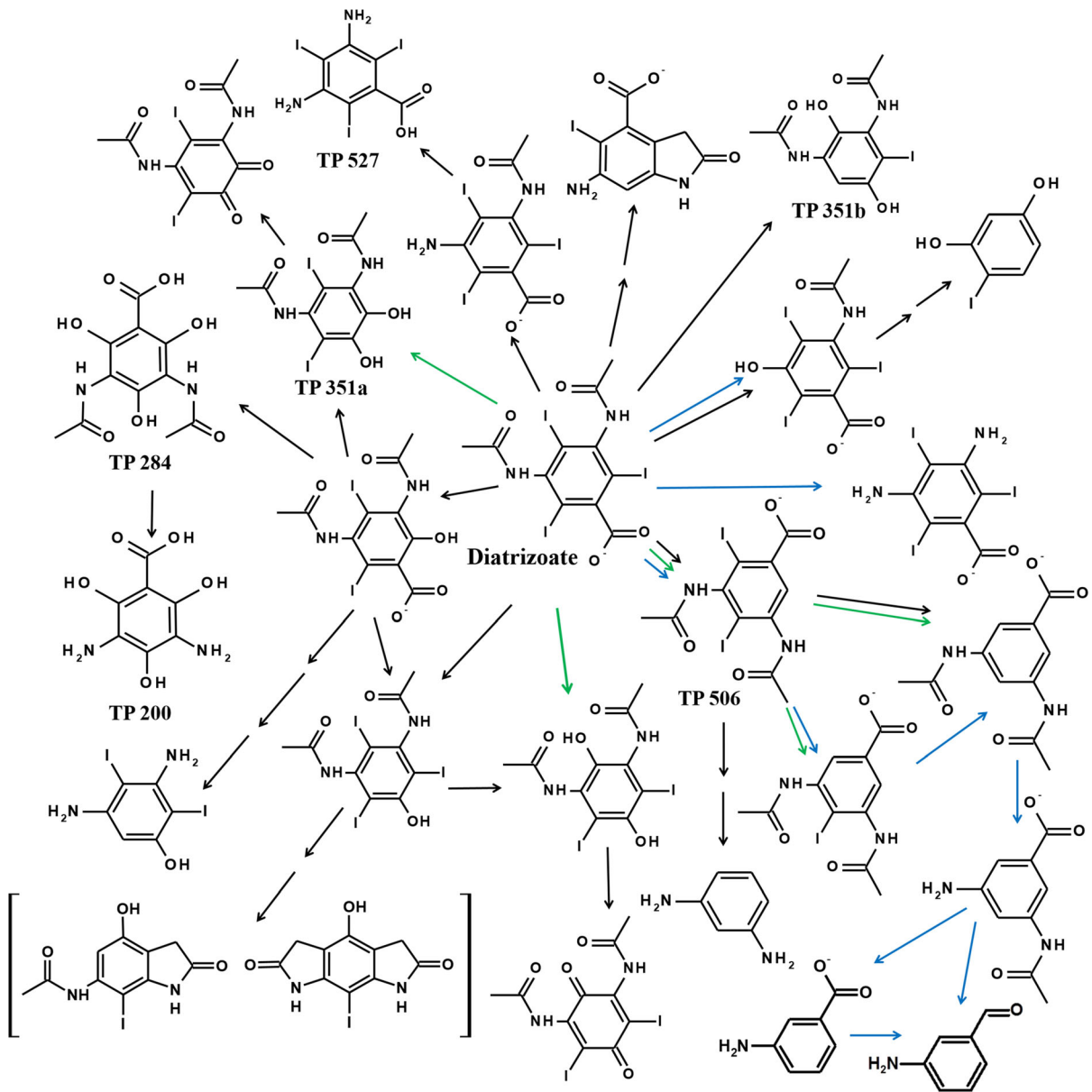
The doses given are recommended for adults by manufacturers. The dose range depends on the type of medical examination. logP—the logarithm of the ratio of the concentrations of a solute between the two solvents; pKa—an acid dissociation constant, P—the octanol/water partition coefficient

erythromycin, clarithromycin, azithromycin on the Watch List of substances that should be strictly monitored in surface waters of the EU. This was the first document to include pharmaceutical substances with unquestionable therapeutic activity but posing a potential threat to the environment (Directive 2013/39/EU). The Watch List is regularly updated and currently it also contains other pharmaceuticals such as antibiotics: amoxicillin and ciprofloxacin. It is also worth emphasizing that after the last revision, diclofenac was removed from this list (Commission Implementing Decision (EU) 2018/840).

Studies of hospital sewage composition indicate that they can be 60% loaded with active pharmaceutical compounds; these compounds are not effectively removed by wastewater treatment plants, and therefore, are often present in effluents released to the surface waters (Giannakis et al. 2017). One of the groups of such compounds is iodinated X-ray contrast media (ICM), which usually constitutes over 3% of all pharmaceuticals detected in the water (Giri and Pal 2014). ICM are derivatives of 2,4,6-triiodinated benzoic acid used as ionic (with a carboxylate-containing benzene substituent) or non-ionic (without a carboxylate-containing benzene substituent) monomers and dimers. The dimers consist of two triiodinated benzene rings linked by an organic functional group. The structure of ICM plays a dual role. Three large iodine

atoms covalently bonded to a benzene ring are in close proximity to each other, which enhances the effective molecular size attenuating X-rays. Additionally, the covalent bonding of iodine atoms to a stable benzene ring reduces the risk of the toxic effect of free iodide. The ICM are used as positive contrast agents in computed tomography and magnetic resonance in venography, urography, choleography, and angiography. They are necessary in the imaging of a variety of anatomic structures, including solid organs like kidney or extremities, body cavities (e.g., abdominal cavity) or vasculature (Bottinor et al. 2013; Beckett et al. 2015). In 2016, half of the 200 million patient examinations in Europe and the US were conducted using contrast agents for accurate diagnoses (OECD Health Statistics).

The constantly increasing incidence of chronic and complex comorbidities, as well as the rising aging population and the incidence of cancer lead to an increase in the number of diagnostic imaging tests. According to the market research reports prepared by the Markets and Markets Research Private Ltd (2020) for forecast period 2020–2024 and the Grand View Research (2020) for 2020–2027, the size of the global contrast media market was USD 5.23 billion in 2019 and is expected to reach USD 6.0 billion by 2024 and USD 6.9 billion by 2027. In 2019, iodinated contrast agents accounted for the largest market share of 67.2%



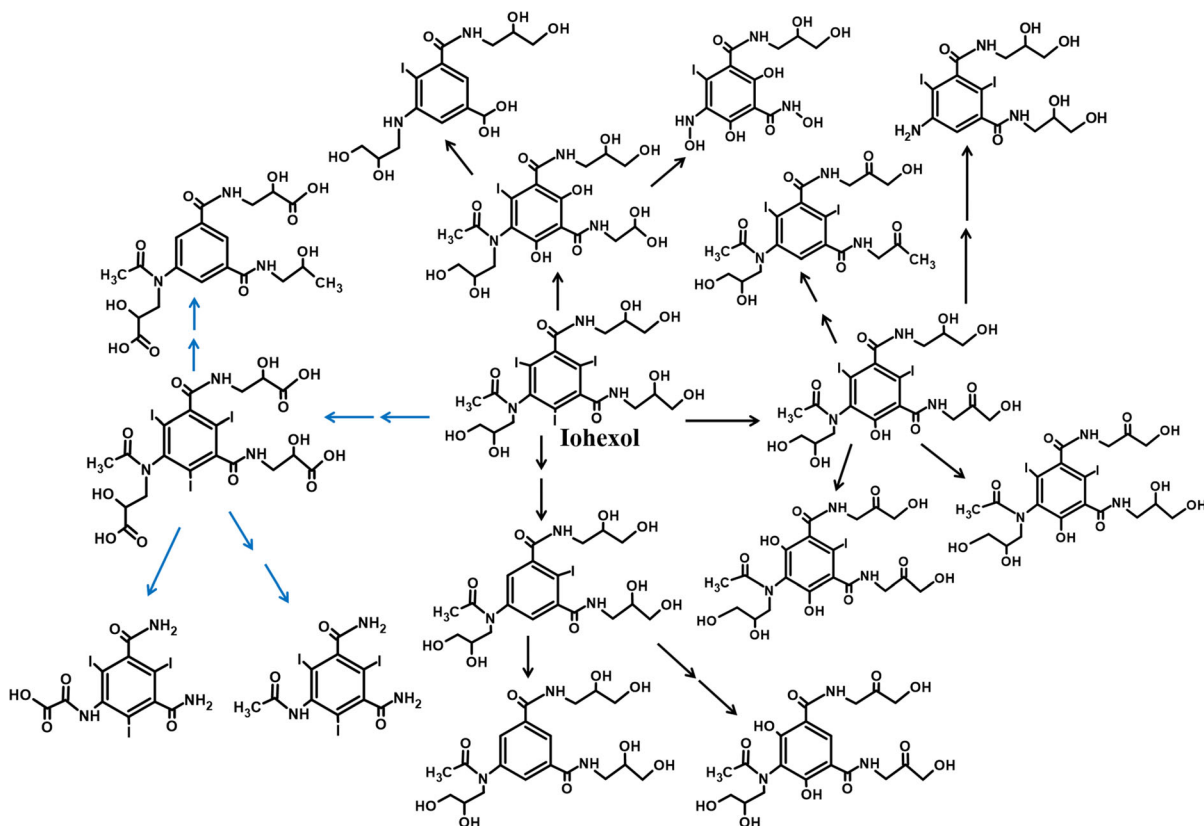
**Fig. 1** Proposed transformation pathways of diatrizoate treated with AOPs (black arrows), during water disinfection (green arrows) and in the presence of microorganisms (blue arrows)

(Jeong et al. 2010; Velo-Gala et al. 2012; Hapeshi et al. 2013; Rastogi et al. 2014; Del Moro et al. 2015; Radjenovic and Petrovic 2016; Zhou et al. 2017). (Color figure online)

in North America and 25.1% in Europe. Despite the lack of such data for Asia, the Asia Pacific market (Japan, China, India, Korea and other) is expected to register the highest growth during the forecast period from 2020 to 2024.

Nowadays, the most commonly used ICM are ionic diatrizoate (3,5-diacetamido-2,4,6-triiodobenzoic acid) and non-ionic iohexol (5-[N-(2,3-

dihydroxypropyl)acetamido]-2,4,6-triiodo-N,N'-bis(2,3-dihydroxypropyl)isophthalamide), iomeprol (N,N'-bis(2,3-dihydroxypropyl)-2,4,6-triiodo-5-(N-methylglycolamido) isophthalamide), iopamidol (N,N'-bis[2-hydroxy-1-(hydroxymethyl)ethyl]-2,4,6-triiodo-5 lactamidoisophthalamide) and iopromide (N,N'-Bis(2,3-dihydroxypropyl)-2,4,6-triiodo-5-(2-methoxyacetamido)-N-methylisophthalamide). Diatrizoate was first approved



**Fig. 2** Proposed transformation pathways of iohexol treated with AOPs (black arrows) and in the presence of microorganisms (blue arrows) (Jeong et al. 2010; Kormos et al. 2010; Hapeshi et al. 2013; Giannakis et al. 2017). (Color figure online)

for medical purposes in the US in 1954. It is a high-osmolality contrast agent (1550 mOsm/kg) and hypertonic to blood; therefore, its intravascular administration is reduced due to the risk of adverse reactions. Nowadays, diatrizoate is reserved for direct pyelography, cholangiography, cystography, and urethrography (Thomsen and Dorph 1993; Andreucci et al. 2014). The development of non-ionic, low-osmolar ICM has greatly reduced the incidence of adverse reactions to contrast media. A good example is iomeprol, a non-ionic contrast agent of the latest generation released by Bracco UK Ltd in 1995. In contrast to iohexol, it has lower chemotoxicity, osmolality (730 mOsm/kg), and viscosity and higher water solubility. Moreover, iomeprol solutions are chemically stable and do not contain chelating agents (e.g., EDTA), which can cause adverse haemodynamic and electrophysiological effects (Dooley and Jarvis 2000). Similar to iomeprol, iopamidol is highly soluble in water, with very low toxicity; therefore, it is used as a safe intrathecal contrast medium in pediatrics

(Wells et al. 1988; Aime et al. 2005). In turn, low-osmolar, non-ionic iopromide is a water-soluble X-ray contrast agent for intravascular administration (Mruk 2016). The average doses of the appropriate ICM for adults vary and depend on the patient's body weight and the type of examination. For example, according to the Bracco UK Ltd recommendations, the dose of iomeprol (trade name—Iomeron 400) ranges from 0.11 g for urography to 139 g for computed tomography and angiocardiology. Recommended doses and the physicochemical properties of the five ICM discussed above are presented in Table 1.

The stable structure of ICM is a main reason for their recalcitrance and high persistence, leading to their accumulation in the environment. They are present in surface water and groundwater at concentrations ranging from ng/L to µg/L (Sacher et al. 2001). However, only iopromide was recognized by the Globally Harmonized System of Classification and

**Table 2** Transformation efficiency of selected ICM depending on their concentration and the physicochemical environmental conditions

Initial ICM conc., mg/L	Treatment	Reagents	Transformation efficiency, %	References
<i>Diatrizoate</i>				
288.7	$\gamma$ Irradiation	$\cdot\text{OH}$ , $e^-_{aq}$	40	Jeong et al. (2010)
25	$\gamma$ Irradiation	$\cdot\text{OH}$ , $e^-_{aq}$ , $\text{H}^+$	91.9	Velo-Gala et al. (2012)
12.7	Electrolysis	$\text{Na}_2\text{SO}_4$	79	Radjenovic and Petrovic (2016)
		$\text{NaNO}_3$	86	
63.59	Electrolysis	$\cdot\text{OH}$	> 90	Bocos et al. (2016)
70	Electrolysis	$\text{NaClO}_4$ ,	> 85	Del Moro et al. (2015)
		$\text{Na}_2\text{SO}_4$	> 80	
30	UV radiation	$\text{SO}_4^{\cdot-}$	84	Zhou et al. (2017)
0.1	Chlorination	$\text{NH}_2\text{Cl}$ , $\text{ClO}_2$ , $\text{NaClO}$	0	Wendel et al. (2014)
<i>Iohexol</i>				
328–410	$\gamma$ Irradiation	$\cdot\text{OH}$ ,	79 $\pm$ 6	Jeong et al. (2010)
		$e^-_{aq}$	81 $\pm$ 16	
8.2–821	UV radiation	$\text{H}_2\text{O}_2$ , $\text{Fe}^{2+}$	> 90	Giannakis et al. (2017)
0.1	Chlorination	$\text{NH}_2\text{Cl}$ , $\text{ClO}_2$ , $\text{NaClO}$	0	Wendel et al. (2014)
<i>Iopromide</i>				
316–396	$\gamma$ irradiation	$\cdot\text{OH}$ ,	71	Jeong et al. (2010)
		$e^-_{aq}$	87	
15.8	Electrolysis	$\text{Na}_2\text{SO}_4$	46	Radjenovic and Petrovic (2016)
		$\text{NaNO}_3$	75	
70	Electrolysis	$\text{NaClO}_4$ , $\text{Na}_2\text{SO}_4$	> 85	Del Moro et al. (2015)
			> 80	
0.1	Chlorination	$\text{NH}_2\text{Cl}$ , $\text{ClO}_2$ , $\text{NaClO}$	0	Wendel et al. (2014)
<i>Iopamidol</i>				
311–389	$\gamma$ Irradiation	$\cdot\text{OH}$ ,	73	Jeong et al. (2010)
		$e^-_{aq}$	75	
70	Electrolysis	$\text{NaClO}_4$	> 85	Del Moro et al. (2015)
		$\text{Na}_2\text{SO}_4$	> 80	
7.8	UV radiation	$\text{Fe}_2(\text{C}_2\text{O}_4)_3$ , $\text{H}_2\text{O}_2$	95	Zhao et al. (2014)
0.1	Chlorination	$\text{NH}_2\text{Cl}$	7.9	Wendel et al. (2014)
		$\text{ClO}_2$	0	
		$\text{NaClO}$	42–100	
<i>Iomeprol</i>				
1–389	$\gamma$ Irradiation	$\cdot\text{OH}$ ,	68	Jeong et al. (2010)
		$e^-_{aq}$	78	
70	Electrolysis	$\text{NaClO}_4$	> 85	Del Moro et al. (2015)
		$\text{Na}_2\text{SO}_4$	> 80	
0.1	Chlorination	$\text{NH}_2\text{Cl}$ , $\text{ClO}_2$ , $\text{NaClO}$	0	Wendel et al. (2014)

Labelling of Chemicals (GHS) as an environmental hazard identified by the code H410, meaning that it is very toxic to aquatic life with long-lasting effects. The

identification and quantification of ICM and their transformation products is a big challenge, especially when they are present in only trace amounts.

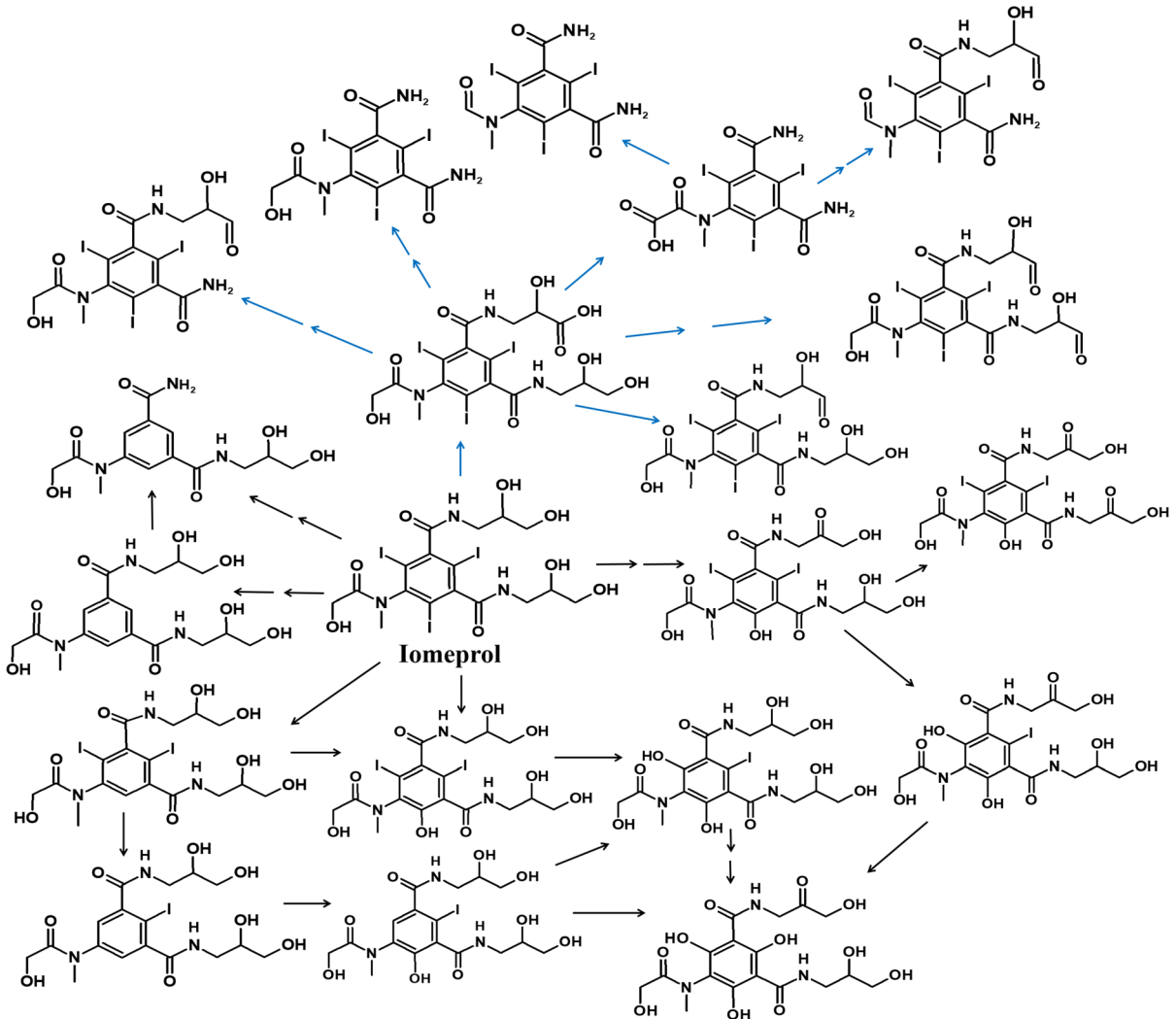
**Table 3** Biotransformation efficiency of selected ICM depending on their concentration and the physicochemical and biological environmental conditions

Initial ICM conc., mg/L	Material	Conditions	Biotransformation efficiency, %	References
<i>Diatrizoate</i>				
0.2	Activated sludge	Aerobic, MBBR	0	Casas et al. (2015)
10	Soil, groundwater	Anaerobic/aerobic	> 95	Redeker et al. (2014)
10	Urban wastewater	Aerobic, MBBR	73	Hapeshi et al. (2013)
10–35	Activated sludge, river water and sediment	Anaerobic/aerobic	0–95	Kalsch (1999)
1000	Soil and river sediment	Anaerobic/aerobic	0	Kormos et al. (2010)
1860	Activated sludge	Aerobic	100	Haiß and Kümmerer (2006)
<i>Iohexol</i>				
0.2	Activated sludge	Aerobic, MBBR	60–80	Casas et al. (2015)
10	Urban wastewater	Aerobic, MBBR	79	Hapeshi et al. (2013)
1000	Soil and river sediment	Aerobic	> 95	Kormos et al. (2010)
<i>Iopromide</i>				
0.2	Activated sludge	Aerobic, MBBR	0	Casas et al. (2015)
12	<i>Trametes versicolor</i> , synthetic sewage	Aerobic	65.4	Gros et al. (2014)
45	Activated sludge, river water and sediment	Anaerobic/aerobic	85–95	Kalsch (1999)
30	Sewage with <i>Pseudomonas</i> sp. I-24	Starch as additional carbon source, anaerobic-anoxic/aerobic	61.3–95	Liu et al. (2013)
30	<i>Pseudomonas</i> sp. I-24	Liquid batch culture, starch as additional carbon source	88.24	Xu et al. (2014)
1000	Soil and groundwater	Aerobic	> 90	Shulz et al. (2008)
1000	Nitrifying activated sludge	Aerobic	61	Batt et al. (2006)
<i>Iopamidol</i>				
0.2	Activated sludge	Aerobic, MBBR	60–80	Casas et al. (2015)
1000	Soil and river sediment	Aerobic	50 > 95	Kormos et al. (2010)
<i>Iomeprol</i>				
0.2	Activated sludge	Aerobic, MBBR	60–80	Casas et al. (2015)
200	<i>P. fluorescens</i> AR 11	Anoxic/ aerobic, batch culture, static column, flow-through microcosm	10–42	Hack et al. (2015)

**Table 3** continued

Initial ICM conc., mg/L	Material	Conditions	Biotransformation efficiency, %	References
1000	Soil and river sediment	Aerobic	> 95	Kormos et al. (2010)

*MBBR* moving bed biofilm reactor

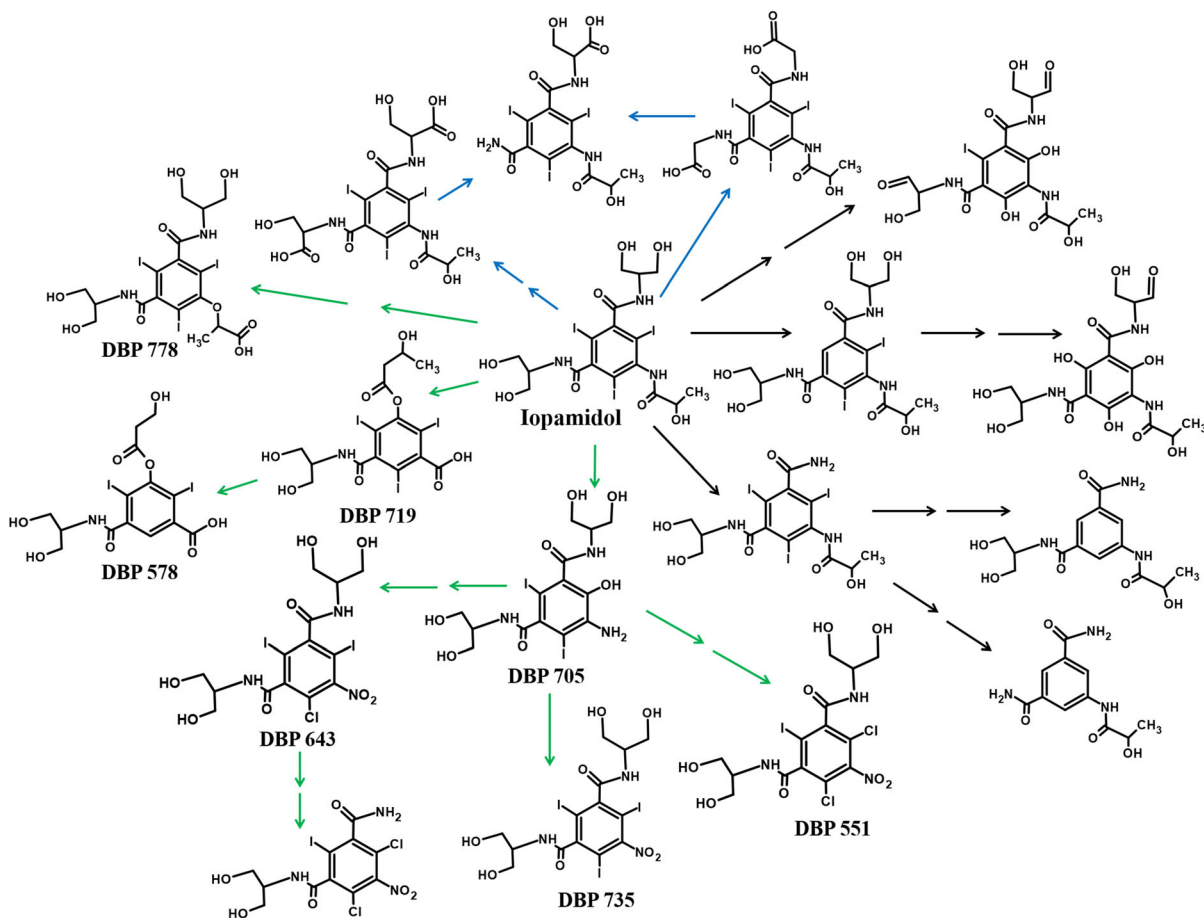


**Fig. 3** Proposed transformation pathways of iomeprol treated with AOPs (black arrows), during water disinfection (green arrows) and in the presence of microorganisms (blue arrows) (Jeong et al. 2010; Kormos et al. 2010; Del Moro et al. 2015). (Color figure online)

Identification and quantification therefore require advanced sensitive analytical methods such as high-performance liquid chromatography with tandem mass spectrometry (HPLC/MS) and ion chromatography. Monitoring the occurrence and fate of ICM is

necessary because their continuous input to surface and groundwater, even at low concentrations, may constitute a long-term potential risk for living organisms. Because of scarce information about the impact of ICM on ecosystems concerning chronic toxicity,





**Fig. 4** Proposed transformation pathways of iopamidol treated with AOPs (black arrows), during water disinfection (green arrows) and in the presence of microorganisms (blue arrows)

(Jeong et al. 2010; Kormos et al. 2010; Wendel et al. 2014; Zhao et al. 2014; Del Moro et al. 2015). (Color figure online)

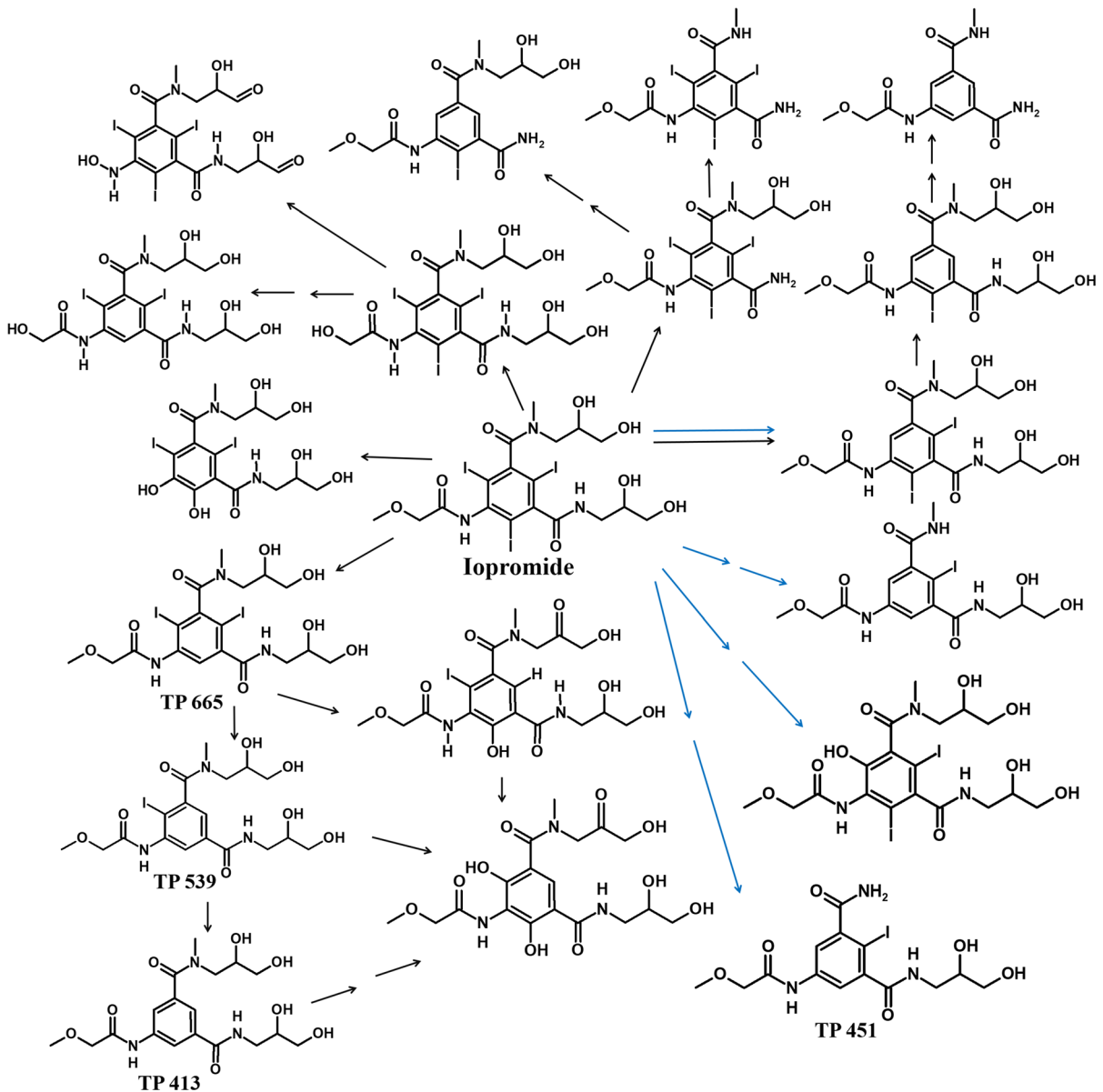
more studies are needed in order to prevent possible future threats.

This review summarizes current knowledge about (1) (bio)transformation of ICM in wastewater, water, sediments, and soil, (2) formed by-products that are dependent on physicochemical and environmental conditions, and (3) the toxicity of ICM and their by-products to living organisms.

## 2 Transformation of ICM

A single dose of ICM during the examination of a patient is up to 200 g (Wendel et al. 2014; Matsushita et al. 2015). After the test, the compounds are excreted unchanged from the body within 24 h and discharged into wastewater. Because of their complex chemical

structure, ICM can remain unchanged or they can be transformed in a conventional wastewater treatment plant (WWTP) into various products through physical, chemical or biological processes, which are discussed in the following subsections of this chapter. Consequently, the unchanged ICM and their by-products can enter surface water, groundwater, and even in drinking water at concentrations up to 100 µg/L (Duirk et al. 2011; Wendel et al. 2014). It was reported that iohexol, iomeprol, iopamidol, and iopromide in wastewater, river water, groundwater and drinking water generated approximately 46 different ICM transformation products (TPs), which were detected mainly during biological treatment of wastes (Kormos et al. 2011). Among them, iopamidol proved to be the most persistent in wastewater, with a transformation efficiency of 35%, whereas iohexol, iomeprol, and



**Fig. 5** Proposed transformation pathways of iopromide treated with AOPs (black arrows) and in the presence of microorganisms (blue arrows) (Schulz et al. 2008; Jeong et al. 2010; Del Moro et al. 2015; Radjenovic and Petrovic 2016). (Color figure online)

iopromide were less stable, and they were eliminated with efficiencies of 85–90%. In total, 26 TPs were detected in WWTP effluents. Furthermore, iomeprol generated the highest concentration of TPs, in the range of 120 ng/L (TP 701) to 500 ng/L (TP 687), which were measured during bank filtration and granular activated carbon filtration at a drinking water treatment plant, although the concentration of

iomeprol alone was very low, about 11 ng/L (Kormos et al. 2011).

## 2.1 Advanced oxidation processes in ICM degradation

Numerous physical and chemical treatments like membrane filtration, coagulation, flotation, electrolysis, and ozonation have been introduced into WWTPs

to handle a wide spectrum of wastes. Among them, advanced oxidation processes (AOPs) utilising reactive species involving hydroxyl ( $\cdot\text{OH}$ ) or sulphate ( $\text{SO}_4^{\cdot-}$ ) radicals are considered to be the most effective methods for destroying the structure of ICM (Ikehata et al. 2006; Giannakis et al. 2017). Although AOPs have an obvious advantage in eliminating ICM over biological methods, they are not commonly used in conventional sewage treatment plants (Oliva et al. 2018). It should be emphasized that to date the overwhelming majority of experiments have been carried out under laboratory conditions using synthetic media, which does not reflect the real conditions in sewage treatment plants. One of the main reasons for this is high cost of this procedure on an industrial scale (Dewil et al. 2017). Another reason is the lack of applicable regulations regarding the need to monitor the concentration and fate of ICM and their by-products during the wastewater treatment process.

In the presence of the reactive radicals, both ionic and non-ionic ICM are deiodinated and their side chains are transformed through similar reactions. However, their degradation efficiencies are different and depend on the experimental conditions (Table 2). In water solutions of ionic diatrizoate treated by  $\gamma$ -irradiation (Jeong et al. 2010; Velo-Gala et al. 2012), Fenton's reagents, iron(III), iron(II) salts and UV radiation (Velo-Gala et al. 2014; Bocos et al. 2016), the main dehalogenation reaction in plausible degradation pathways is an ipso attack of  $\cdot\text{OH}$  on the iodine site. As a result, the iodine is substituted by the addition of a hydroxyl group and finally 3,5-diacetamide-2,4,6-trihydroxybenzoic acid (TP 284) (Fig. 1) is formed. Furthermore, diatrizoate or its deiodinated derivatives can undergo a deacetylation reaction to form amine derivatives [3,5-diamino-2,4,6-trihydroxybenzoic acid (TP 200) or 3,5-diamino-2,4,6-triiodinebenzoic acid (TP 527)]. Another plausible reaction is oxidative decarboxylation via  $\cdot\text{OH}$ , thus giving a phenolic product (Fig. 1). Further ring cleavage leads to the formation of short-chain carboxylic acids (Bocos et al. 2016).

Iohexol is another model non-ionic ICM that has been subjected to extensive investigation using AOPs, including UV, UV/ $\text{H}_2\text{O}_2$ , UV/ $\text{H}_2\text{O}_2/\text{Fe}^{2+}$  treatment and  $\gamma$ -irradiation (Jeong et al. 2010; Giannakis et al. 2017). Based on the identified intermediates of iohexol degradation, several parallel reactions are postulated to obtain more polar by-products. The ipso attack of

$\cdot\text{OH}$  at the iodo site with further oxidation by this radical results in the formation of deiodinated products and dissociative electron attachment, yielding a deiodinated product and  $\cdot\text{OH}$ , giving a phenolic compound. In further steps, amine or ketone products are produced after decarboxylation and hydrogen abstraction from side chains, respectively (Fig. 2) (Jeong et al. 2010; Giannakis et al. 2017). Other non-ionic ICM such as iopromide, iopamidol or iomeprol are degraded through reactions similar to those of iohexol. Literature shows, that the transformation of iopromide and iopamidol treated by AOPs generates the formation of about 30 different TPs, whereas during the transformation of iomeprol, about 20 TPs are formed (Fig. 3) (Schulz et al. 2008; Jeong et al. 2010; Kormos et al. 2010; Wendel et al. 2014; Zhao et al. 2014; Del Moro et al. 2015; Radjenovic and Petrovic 2016). In one of the proposed transformation pathways, the one side chain of iomeprol is reduced to an amide, whereas the easiest form of iopamidol contains two side chains, which are transformed to amides (Fig. 4). The shortest identified side chains of iopromide are hydroxyl or amine groups (Fig. 5).

## 2.2 Effect of water disinfection on ICM transformation

Because ICM are not effectively removed during wastewater treatment, they are released into water, becoming an additional source of iodine in reservoirs of drinking water. Because even low concentrations of ICM can generate undesired by-products during the disinfection of raw water, the fate of iodine released during ICM deiodination is crucial. In addition to the most-often detected disinfection by-products (DBPs) such as chloroform, dichloroacetonitrile, trichloroacetic acid, and dichloroacetic acid, different iodinated disinfection by-products (I-DBPs) in the presence of iodine could be formed. One of the most undesirable groups of I-DBPs during ICM oxidation in water are iodo-trihalomethanes (I-THMs), which impart a nasty odour and taste to drinking water. Their organoleptic threshold concentration in water can be as much as  $0.03 \mu\text{g/L}$  (Bichsel and von Gunten 2000). During the first step of disinfecting raw water, iodine in the presence of chlorine or chloramine is quickly oxidized to hypoiodous acid (HOI), which reacts with organic matter to produce the I-THMs (especially  $\text{CHI}_3$ ). The formation of  $\text{CHI}_3$  during oxidative drinking water

treatment is influenced by the physicochemical parameters of the treated water, such as temperature, pH, iodine concentration, type and concentration of organic matter and the stability of the oxidant (Bichsel and von Gunten 2000). Research by Ye et al. (2014) indicated that the formation of I-THMs during chlorination and chloramination of raw water containing iopamidol, iopromide, iodixanol, iohexol, and diatrizoate collected from the intake of the Yangshupu drinking water treatment plant (Shanghai, China) depended on the presence and concentration of chlorine and monochloramine. The chloramination of water generated more mixed I-THMs than chlorination. For example, after the addition of  $\text{NH}_2\text{Cl}$  at concentrations of 200 and 250  $\mu\text{M}$  into water containing iopamidol, six different I-THMs ( $\text{CHI}_3$ ,  $\text{CHBrI}_2$ ,  $\text{CHClI}_2$ ,  $\text{CHBr}_2\text{I}$ ,  $\text{CHBrClI}$ ,  $\text{CHCl}_2\text{I}$ ) were identified, whereas in the presence of  $\text{Cl}_2$  at the same concentrations only three I-THMs ( $\text{CHClI}_2$ ,  $\text{CHCl}_2\text{I}$ ,  $\text{CHBrClI}$ ) were detected. The highest total concentrations of I-THMs in chlorinated and chloraminated water were 276 and 254 nM, respectively. The concentrations of I-THMs formed during chlorination and chloramination of water containing the other ICM were significantly lower. In the chlorinated water, the concentrations did not exceed 100 nM, whereas in the chloraminated water, it was about 200 nM. Depending on the increase in the concentrations of I-THMs detected during water chlorination and chloramination, the ICM tested can be ordered as follows: iopamidol > iohexol > iodixanol > diatrizoate > iopromide and iopamidol > diatrizoate > iodixanol > iohexol > iopromide.

In addition to classifying the I-THMs as small chlorinated DBPs, stable chlorinated DBPs with higher molecular weights and containing benzene rings can also appear during the disinfection of water. Interestingly, the formation of I-THMs is not correlated with the total formation of I-DBPs (Allard et al. 2016). Iopromide photodecomposition followed by chlorination or chloramination indicated a decrease in the amount of I-DBPs in the presence of  $\text{HOCl}$  in the concentration range of 1–5 mg  $\text{Cl}_2/\text{L}$ . In turn, iodine incorporation into I-THMs increased in the presence of 2 mg  $\text{Cl}_2/\text{L}$  and decreased in the presence of 5 mg  $\text{Cl}_2/\text{L}$  ( $\text{CHCl}_3$  dominated in the mixture of THMs). The presence of  $\text{NH}_2\text{Cl}$  in the concentration range of 1–5 mg  $\text{Cl}_2/\text{L}$  did not influence the amount of the I-DBPs, but it caused an increase in the concentrations

of the I-THMs (mainly  $\text{CHI}_3$ ). In the presence of aqueous chlorine, five different reactions during transformation of the I-DBPs were observed: cleavage of side chains or their inversion, exchange of iodine by chlorine, amide hydrolysis and oxidation of amine to a nitro group (Wendel et al. 2014, 2016). During the disinfection of water containing iopamidol, five different high-molecular weight I-DBPs with molecular masses of 778, 705, 735, 643 and 551 Da were identified (Fig. 4) (Wendel et al. 2014, 2016). I-DBP 705 appeared after deacylation of one side chain of iopamidol; however, I-DBP 735 was identified after the oxidation of an amine to a nitro group in the rest of this side chain. I-DBP 643 and I-DBP 551 were formed after replacing iodine with chlorine, followed by the oxidation of  $-\text{NH}_2$  to  $-\text{NO}_2^-$  in I-DBP 705. I-DBP 778 was a product of inversion of the side chain followed by amide hydrolysis. It should also be pointed that the oxidative-coupling reactions between primary amines like DBP 705 could also lead to the formation of dimers (DBP 1406) (Wendel et al. 2014). In total, about 20 different high-molecular weight I-DBPs were identified during the transformation of iopamidol (Fig. 3). Interestingly, the efficiency of the transformation (0.1 mg/L) in the presence of hypochlorite, monochloramine and chlorine dioxide (3 mg/L) ranged from 0% (in the presence of  $\text{ClO}_2$ ) through 8% (with  $\text{NH}_2\text{Cl}$ , pH 8.5) to 100% (with  $\text{NaClO}$ , pH 8.5). However, the transformation of diatrizoate, iohexol, iopromide and iomeprol under the same conditions was not observed (Table 2).

### 2.3 Biotransformation of ICM

Despite many studies, the biological transformation/degradation of ICM is still poorly understood and described in the literature. Among bacteria, only two strains, *Pseudomonas* sp. I-24 and *Pseudomonas fluorescens* AR11, were reported as iopromide- and iomeprol-degraders, respectively (Liu et al. 2013; Xu et al. 2014; Hack et al. 2015). *Pseudomonas* sp. I-24 was isolated from the activated sludge of a wastewater treatment plant in Shanghai, and it was able to co-metabolize iopromide (Liu et al. 2013). Interestingly, an inoculation of this bacterium into wastewater contaminated with iopromide (15  $\mu\text{g}/\text{L}$ ) significantly enhanced the removal efficiency of ICM from 29.8% in the control wastewater to 61.3% in the bioaugmented wastewater. Although *Pseudomonas* sp. I-24

has been identified as capable of degrading iopromide, the pathway of its biodegradation, including intermediates and the enzymes involved in the transformation of the formed compounds, has not been described yet. The second bacterial strain, *P. fluorescens* AR11, which is capable of degrading iomeprol, did not originate from a source in contact with ICM, it was isolated from raw milk during cheese production (Hack et al. 2015). It was able to remove iomeprol (390 mg/L) from a nutrient solution mixed with sand in batch experiments under aerobic and anoxic conditions with maximum efficiencies of 42% and 10%, respectively, within 30 days. However, despite the high concentration of TPs in the culture, it was found that the iomeprol was not completely degraded by this bacterium. Similar to *Pseudomonas* sp. I-24, the forming TPs and enzymes engaged in iomeprol degradation by *P. fluorescens* AR11, as well as the complete degradation pathways, remain unknown.

The second group of microorganisms that are recognized to be capable of transforming ICM is white rot fungi. The fungi are able to oxidize a variety of organic contaminants due to secretion of extracellular ligninolytic enzymes. The non-specificity of free radical-mediated lignin peroxidases, manganese-dependent peroxidases and laccases enable fungi to transform a large number of haloaromatic compounds (Hatakka and Hammel 2011; Rodríguez-Couto 2017). One of the potential degraders of diatrizoate and iopromide is *Trametes versicolor*, a common species found throughout the world. A study by Rode and Müller (1998) clearly indicated that the initial transformation and partial deiodination of diatrizoate (614 mg/L) by *T. versicolor* in batch cultures were catalysed by fungal extracellular peroxidases and laccases. The metabolites of these transformations (i.e., TP 506—Fig. 1) at concentrations corresponding to half the diatrizoate disappearance were determined and identified after 14 days. The authors suggested that in addition to the reductive diiodination, an additional process may occur, such as polymerization of intermediate metabolites to forms that can not be detected by HPLC. In another study, Gros et al. (2014) revealed that the efficiency of iopromide removal by *T. versicolor* reached 65.4% (0.4 mg/L) in hospital wastewater and 62% (12 mg/L) in liquid synthetic medium within 5 and 7 days, respectively. Additionally, the identification of eight different transformation products may indicate that they were formed through

sequential deiodination (TP 665, 539, 413) and N-dealkylation of the amide at the hydroxylated side chain of the molecule (TP 451) (Fig. 5).

Nowadays, special attention is focusing on the biodegradation of ICM by a mixed population of microorganisms present in activated sludge, soil, river sediment and groundwater, where ICM concentrations reach values from 0.2 to 1860 mg/L (Table 3). It is well known that an individual microorganism can generally metabolize only a limited range of substrates. The biodegradation/biotransformation of many recalcitrant pollutants is easier when more than a single species cooperates with each other. A defined consortia of microorganisms equipped with broad enzymatic capacities usually increases the rate and extent of contaminant biodegradation/biotransformation. Some members of the microbial community have the ability to secrete important degradative enzymes and growth factors, whereas others can increase their solubility or bioavailability. Therefore, mixed bacterial and fungal populations can degrade pollutants more effectively and in shorter times than single microbial strains. From a practical point of view, the cooperation of fungal–bacterial co-cultures degrade aromatic xenobiotics by breaking ring structures using fungal extracellular ligninolytic enzymes and further metabolism of the formed intermediates by bacteria (Mikesková et al. 2012; Sheng et al. 2017). This phenomenon has been observed during biodegradation of polycyclic aromatic hydrocarbons (Boonchan et al. 2000; Machín-Ramírez et al. 2010), polychlorinated biphenyls (Fernández-Sánchez et al. 2001) and azo dyes (Gou et al. 2009). In the literature concerning the biodegradability of ICM, the particular microbial groups or species in mixed consortia engaged in this process are not identified and characterized (Kormos et al. 2010; Zhang et al. 2016). Information in this field is still therefore very limited and refers only to the participation of nitrifying bacteria in enhancing ICM removal from activated sludge (Batt et al. 2006; Torresi et al. 2016). For example, Batt et al. (2006) reported that the efficiency of iopromide removal (0.10–0.27 µg/L) in nitrifying activated sludge reached 61%, whereas in conventional activated sludge, it was negligible.

In addition to the microbial activity, the biotransformation efficiency of ICM also depends on abiotic factors, such as the structure, concentration and properties of the biotransformed compound, as well

as the physicochemical conditions of the environmental matrices. A comparison of the biodegradability of diatrizoate and iohexol, which differ significantly in structure and properties (Table 1), in a moving bed biofilm reactor (MBBR) clearly indicated that diatrizoate was less susceptible to degradation than iohexol. The efficiency of diatrizoate (10 mg/L) transformation within 5 days was 50%, whereas iohexol was biotransformed under the same conditions with an efficiency of 70%. Although the efficiencies of biotransformation were different, the number of formed intermediates was similar (13–14 TPs). For this reason, it could be expected that TPs form through several competing pathways, mainly through hydroxylation, deacetylation, deiodination, deamination and fully dehalogenated main end product (Figs. 1, 2) (Hapeshi et al. 2013). A comparison of the biodegradability of diatrizoate and iopromide in river water plus sediment also showed that ionic diatrizoate was hardly biotransformed but the non-ionic iopromide was transformed (Kalsch 1999) (Table 3). Under the same conditions, diatrizoate (35 mg/L) and iopromide (45 mg/L) were biotransformed with an efficiency of 90% over 50 days and 50 h, respectively. Nevertheless, mineralization of the tested ICM to carbon dioxide was not observed. The weaker biodegradability of diatrizoate compared to ionic ICM could be explained by the steric hindrance between the large iodine atoms and the remaining short side chains of this compound.

Some published data have indicated that the biodegradability of ionic iohexol, iomeprol and iopamidol might also differ (Kormos et al. 2010; Casas et al. 2015). Experiments in aerobic soil–water and river sediment–water batch systems implied that iohexol and iomeprol were more effectively biotransformed in comparison with iopamidol (Kormos et al. 2010). Under experimental conditions, more than 90% of the initial concentrations of iohexol and iomeprol were biotransformed within 49 days, whereas similar iopamidol loss occurred within 100 days (Table 3). The numbers of intermediates formed were also different. During the biotransformation of iohexol (Fig. 2), iomeprol (Fig. 3), and iopamidol (Fig. 4), 15, 11, and eight TPs were detected, respectively. According to the researchers conducted (Kormos et al. 2010), three types of biochemical reactions can biotransform ICM. The first is oxidation of the primary or secondary alcohol groups catalysed by alcohol and aldehyde dehydrogenases, whereas the second is

decarboxylation by thiamine pyrophosphate-dependent enzymes, like transketolases,  $\alpha$ -keto acid decarboxylases or pyruvate-like decarboxylases. The last one is cleavage of the C–N bond by monooxygenases, alcohol, and aldehyde dehydrogenases or decarboxylases. The activity of similar enzymes was also suggested by Schulz et al. (2008) during a study on iopromide biotransformation in water–soil systems. However, many attempts to isolate and identify enzymes involved in microbial metabolism of ICM have failed. To date, knowledge of the proposed pathways of ICM biotransformation are incomplete and enzymes are not accurately characterized. The type of enzymes and their participation in subsequent stages of biotransformation are mainly proposed based on the structures of the identified TPs, the time sequence of their appearance and fundamental metabolic knowledge.

Physicochemical environmental conditions also affect the biotransformation of ICM. The most important factors are considered to be the availability of oxygen, organic carbon, and photochemical pre-treatment. The importance of oxygen during diatrizoate (10 mg/L) biotransformation in anaerobic soil–water batch systems was indicated by Redeker et al. (2014), who reported that diatrizoate was successively deiodinated and deacetylated through seven identified TPs to 3,5-diaminobenzoic acid as a stable final product. Further biotransformation of this compound was only observed under aerobic conditions. The important role of the availability of dissolved organic carbon in the biotransformation of ICM was confirmed in a model of transport of iomeprol during stream–groundwater interactions (Engelhardt et al. 2014). The transformation of this ICM and its daughter products were simulated as a cometabolic process during organic carbon degradation, the main driver for spatial and temporal changes in redox zonation. Photochemical pre-treatment of polluted wastewater is also needed to enhance the elimination of ICM. An example was the treatment of hospital wastewater containing diatrizoate and iohexol (1 mg/L) by UV irradiation combined with TiO<sub>2</sub>, which resulted in disruption of the chemical structure of ICM and enabled their further transformation using biological processes (Borowska et al. 2015). The removal efficiencies of diatrizoate and iohexol from sewage without photochemical pre-treatment were 38% and 60%, respectively, whereas more than 90% of

diatrizoate and the complete removal of iohexol were recorded after the combined photochemical and biological treatment of wastes.

### 3 Toxicity of ICM and their transformation by-products

Despite the fact that contrast agents are regarded as safe pharmaceuticals, their use in disease diagnosis is not completely risk free for humans. They can cause adverse reactions in patients from mild symptoms to severe, life-threatening reactions. The adverse reactions are classified as acute and late. Acute adverse reactions occur within one hour after injection and they are five times more common after the administration of ionic, monomeric, high-osmolar agents than with low-osmolar agents. The symptoms include injection site pain, nausea, vomiting, urticaria, pruritus, or bronchospasm. The late adverse reactions (> 1 h to 7 days) are mainly manifested with skin reactions as a pruritic maculopapular rash or urticaria after exposure to the non-ionic iso-osmolar dimer. Hypotension and cardiovascular shock are the less common delayed reactions. The renal adverse reaction to contrast media is contrast-induced nephropathy. The incidence of this reaction is less than 5% in patients with normal renal function; however, it can be as much as 50% in those with preexisting renal dysfunction (Thomsen 2011; Pasternak and Williamson 2012; Bottinor et al. 2013). In current practice, low-osmolar non-ionic ICM are used most often for intravascular injections due to less toxicity and fewer side effects than ionic agents. Adverse reactions are observed in approximately 15% and 3% of patients after the use of high-(ionic) and low-osmolality (non-ionic) agents, respectively (Pasternak and Williamson 2012). There are three main factors responsible for the higher toxicity of ionic ICM compared to non-ionic agents: (1) hyperosmolality (osmolality 5–8 times higher than blood), (2) the weakest ability to attenuate X-rays; therefore, they need to be administered in higher concentrations than non-ionic ICM and (3) charged molecules tend to disrupt the electrical potential of cell membranes (Pasternak and Williamson 2012).

The continuous input and persistence of ICM even at trace levels in the environment can have a negative impact on the ecosystem; however, the results of

environmental risk assessment of ICM are not conclusive. Although parent compounds as diatrizoate (Polo et al. 2016), iopromide (Steger-Hartmann et al. 1999), iopamidol and iohexol (Matsushita et al. 2015) are considered to be non-toxic, the results of *in silico* model predictions and toxicity tests of their by-products are ambiguous. The photolytic transformation products of diatrizoic acid, which has a molecular mass 351 (Fig. 1), were predicted to be mutagenic according to Leadscope's Salmonella and chromosome aberration models, as well as genotoxic according to a micronucleus *in vivo* model (Rastogi et al. 2014). Simultaneously, the experimental data of a bioluminescence inhibition test of *Vibrio fischeri* indicated that photodegradation products of diatrizoate (25 mg/L) were more toxic than the parent compound. The tested photodegradation products included 2 TPs formed during treatment of diatrizoate by solar radiation (SR) in the presence of H<sub>2</sub>O<sub>2</sub>, 1 TP using SR/K<sub>2</sub>S<sub>2</sub>O<sub>8</sub> and 2 TPs using an SR/Fenton reaction. The authors indicated that the inhibition of bacterial bioluminescence was proportional to the diatrizoate depletion and by-product formation under all tested conditions (Polo et al. 2016). However, none of the 14 TPs from the microbial transformation of diatrizoate (20 mg/L) was toxic to *Daphnia magna* (Hapeshi et al. 2013). The differences in toxicity of TPs formed during photodegradation and microbial transformation may result from the different chemical structures of the photodegradation products in comparison with biotransformation intermediates (Fig. 1).

It was reported that the chlorination of ICM-containing solutions can also lead to the formation of toxic and mutagenic compounds. The 96-h chlorination of an iopamidol solution (1 mg/L) induced the formation of three mutagenic disinfection DBPs with molecular weights of 578, 643 and 719, respectively (Fig. 4). An Ames assay with *Salmonella typhimurium* TA98 and *S. typhimurium* TA100 indicated that these DBPs induced frameshift mutations rather than base-pair-substitution mutations (Matsushita et al. 2015). Additionally, a mammalian (Chinese hamster ovary) cell chronic cytotoxicity assay confirmed that the chlorination of iopamidol (1 g/L) generated a mixture of cytotoxic DBPs. Median lethal concentration (LC<sub>50</sub>) of the residual DBPs mixture was 332 ng/μL (Wendel et al. 2014). More detailed studies with five isolated iopamidol chlorination DBPs allowed researchers to distinguish between two of the most

cytotoxic DBPs, with respective molecular weights of 551 and 735 (Fig. 3). The  $LC_{50}$  values calculated for DBP 551 and DBP 735 were 0.6 and 0.7 g/L, respectively (Wendel et al. 2016). The formation of toxic I-DBPs also occurred after the chlorination and chloramination of photodecomposed moieties of iopromide (8 mg/L). An *in vitro* toxicity test conducted by Allard et al. (2016) with the AREc32 cell-line with an ARE reporter plasmid coupled to reporter gene encoding luciferase and the redox cycling compound tert-butylhydroquinone (tBHQ) (model inducing agent of ARE-enhanced gene expression) showed that water chloramination with  $NH_2Cl$  (5 mg  $Cl_2/L$ ) generated more toxic I-DBPs than chlorination with HOCl (5 mg  $Cl_2/L$ ). The calculated equivalent concentration (tBHQ-EQ) for non-treated iopromide increased from 4.29 to 20.60  $\mu g/L$  for irradiated iopromide ( $UV_{254}$  4000  $J/m^2$ ) and 55.27  $\mu g/L$  for chloraminated iopromide. It was also proved that the addition of organic matter led to the formation of an increasing number of toxic I-DBPs through an increase in the number of reactive sites available for reaction with chlorinated oxidants. Although environmental risk is not expected from the parent compounds of ICM, the toxicological effects associated with the metabolites are confirmed.

#### 4 Conclusions

Although ICM are regarded as safe pharmaceuticals and their use is unquestioned in the diagnosis of diseases, there is a real risk of negative impact of their transformation by-products on the functioning of various ecosystems. In order to prevent a potential threat caused by their presence in the environment, new effective physicochemical and biological methods for their removal should be developed, and more attention should be paid to the transport and fate of parent ICM in the environment. Biological approaches are widely regarded as more economical and environment friendly than physicochemical methods, but their development requires very thorough knowledge about the mechanisms and pathways of ICM degradation. One of the possible future solutions may be the construction of a defined consortia of bacteria and fungi capable of degrading or complementing each other in breaking down individual ICM. Unfortunately, knowledge of the proposed pathways of ICM

biotransformation/biodegradation is still incomplete and the enzymes engaged in these processes have not been identified. Speculations about their activity based on the identified intermediates are important, but they are insufficient to develop a comprehensive and safe method of biological removal of ICM. Therefore, research in this field should be continued and intensified to expand our knowledge about the still poorly understood microbial degradation of ICM.

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#### References

- Aime S, Calabi L, Biondi L, de Miranda M, Ghelli S, Paleari L, Rebaudengo C, Terreno E (2005) Iopamidol: exploring the potential use of a well-established X-ray contrast agent for MRI. *Magn Reson Med* 53:830–834. <https://doi.org/10.1002/mrm.20441>
- Allard S, Criquet J, Prunier A, Falantin C, le Person A, Tang JYM, Croué JP (2016) Photodecomposition of iodinated contrast media and subsequent formation of toxic iodinated moieties during final disinfection with chlorinated oxidants. *Water Res* 103:453–461. <https://doi.org/10.1016/j.watres.2016.07.050>
- Andreucci M, Faga T, Pisani A, Sabbatini M, Russo D, Michael A (2014) Prevention of contrast-induced nephropathy through a knowledge of its pathogenesis and risk factors. *Sci World J* 2014:823169. <https://doi.org/10.1155/2014/823169>
- aus der Beek T, Weber FA, Bergmann A, Hickmann S, Ebert I, Hein A, Küster A (2016) Pharmaceuticals in the environment—global occurrences and perspectives. *Environ Toxicol Chem* 35:823–835. <https://doi.org/10.1002/etc.3339>
- Batt AL, Kim S, Aga DS (2006) Enhanced biodegradation of iopromide and trimethoprim in nitrifying activated sludge. *Environ Sci Technol* 40:7367–7373. <https://doi.org/10.1021/es060835v>
- Beckett KR, Moriarity AK, Langer JM (2015) Safe use of contrast media: what the radiologist needs to know. *Radiographics* 35:1738–1750. <https://doi.org/10.1148/rg.2015150033>



- Bichsel Y, von Gunten U (2000) Formation of iodo-trihalomethanes during disinfection and oxidation of iodide-containing waters. *Environ Sci Technol* 34:2784–2791. <https://doi.org/10.1021/es9914590>
- Bocos E, Oturan N, Sanromán M, Oturan MA (2016) Elimination of radiocontrast agent diatrizoic acid from water by electrochemical advanced oxidation: kinetics study, mechanism and mineralization pathway. *J Electroanal Chem* 772:1–8. <https://doi.org/10.1016/j.jelechem.2016.04.011>
- Boonchan S, Britz ML, Stanley GA (2000) Degradation and mineralization of high molecular weight polycyclic aromatic hydrocarbons by defined fungal–bacterial cocultures. *Appl Environ Microbiol* 66:1007–1019. <https://doi.org/10.1128/aem.66.3.1007-1019.2000>
- Borowska E, Felis E, Żabczyński S (2015) Degradation of iodinated contrast media in aquatic environment by means of UV, UV/TiO<sub>2</sub> process, and by activated sludge. *Water Air Soil Pollut*. <https://doi.org/10.1007/s11270-015-2383-9>
- Bottinor W, Polkampally P, Jovin I (2013) Adverse reactions to iodinated contrast media. *Int J Angiol* 22:149–154. <https://doi.org/10.1055/s-0033-1348885>
- Casas ME, Chhetri RK, Ooi G, Hansen KMS, Litty K, Christensson M, Kragelund C, Andersen HR, Bester K (2015) Biodegradation of pharmaceuticals in hospital wastewater by a hybrid biofilm and activated sludge system (Hybas). *Sci Tot Environ* 530–531:383–392. <https://doi.org/10.1016/j.scitotenv.2015.05.099>
- del Moro G, Pastore C, Di Iaconi C, Mascolo G (2015) Iodinated contrast media electro-degradation: process performance and degradation pathways. *Sci Total Environ* 506–507:631–643. <https://doi.org/10.1016/j.scitotenv.2014.10.115>
- Deo RP, Halden RU (2013) Pharmaceuticals in the built and natural water environment of the United States. *Water* 5:1346–1365. <https://doi.org/10.3390/w5031346>
- Dewil R, Mantzavinos D, Poullos I, Rodrigo MA (2017) New perspectives for advanced oxidation processes. *J Environ Manag* 195:93–99. <https://doi.org/10.1016/j.jenvman.2017.04.010>
- Dooley M, Jarvis B (2000) Iomeprol: a review of its use as a contrast medium. *Drugs* 59:1169–1186. <https://doi.org/10.2165/00003495-200059050-00013>
- Duirk SE, Lindell C, Cornelison CC, Kormos J, Ternes TA, Attene-Ramos M, Osioł J, Wagner ED, Plewa MJ, Richardson SD (2011) Formation of toxic iodinated disinfection by-products from compounds used in medical imaging. *Environ Sci Technol* 45:6845–6854. <https://doi.org/10.1021/es200983f>
- Engelhardt I, Prommer H, Schulz M, Vanderborght J, Schüth C, Ternes TA (2014) Reactive transport of iomeprol during stream–groundwater interactions. *Environ Sci Technol* 48:199–207. <https://doi.org/10.1021/es403194r>
- Fernández-Sánchez JM, Rodríguez-Vázquez R, Ruiz-Aguilar G, Alvarez PJJ (2001) PCB biodegradation in aged contaminated soil: interactions between exogenous *Phanerochaete chrysosporium* and indigenous microorganisms. *J Environ Sci Heal Part A Toxic Hazard Subst Environ Eng* 36:1145–1162. <https://doi.org/10.1081/ESE-100104869>
- Giannakis S, Jovic M, Gasilova N, Gelabert M, Schindelholz S, Furbringer JM, Girault H, Pulgarin C (2017) Iohexol degradation in wastewater and urine by UV-based advanced oxidation processes (AOPs): process modeling and by-products identification. *J Environ Manag* 195:174–185. <https://doi.org/10.1016/j.jenvman.2016.07.004>
- Giri P, Pal C (2014) Ecotoxicological aspects of pharmaceuticals on aquatic environment. *Am J Drug Discov* 1:201400524
- Gou M, Qu Y, Zhou J, Ma F, Tan L (2009) Azo dye decolorization by a new fungal isolate, *Penicillium* sp. QQ and fungal–bacterial cocultures. *J Hazard Mater* 170:314–319. <https://doi.org/10.1016/j.jhazmat.2009.04.094>
- Grand View Research (2020) Contrast media market size, share and trends analysis report by product type (iodinated, gadolinium-based), by application (neurological, cancer, CVDs), by modality (MRI, X-ray/CT), and segment forecasts, 2020–2027
- Gros M, Cruz-Morato C, Marco-Urrea E, Longree P, Singer H, Sarrà M, Hollender J, Vincent T, Rodríguez-Mozaz S, Barceló D (2014) Biodegradation of the X-ray contrast agent iopromide and the fluoroquinolone antibiotic ofloxacin by the white rot fungus *Trametes versicolor* in hospital wastewaters and identification of degradation products. *Water Res* 60:228–241. <https://doi.org/10.1016/j.watres.2014.04.042>
- Hack N, Reinwand C, Abbt-Braun G, Horn H, Frimmel FH (2015) Biodegradation of phenol, salicylic acid, benzenesulfonic acid, and iomeprol by *Pseudomonas fluorescens* in the capillary fringe. *J Contam Hydrol* 183:40–54. <https://doi.org/10.1016/j.jconhyd.2015.10.005>
- Haiß A, Kümmerer K (2006) Biodegradability of the X-ray contrast compound diatrizoic acid, identification of aerobic degradation products and effects against sewage sludge micro-organisms. *Chemosphere* 62:294–302. <https://doi.org/10.1016/j.chemosphere.2005.05.007>
- Hapeshi E, Lambrianides A, Koutsoftas P, Kastanos E, Michael C, Fatta-Kassinos D (2013) Investigating the fate of iodinated X-ray contrast media iohexol and diatrizoate during microbial degradation in an MBBR system treating urban wastewater. *Environ Sci Pollut Res Int* 20:3592–3606. <https://doi.org/10.1007/s11356-013-1605-1>
- Hatakka A, Hammel KE (2011) Fungal biodegradation of lignocelluloses. In: Hofrichter M (ed) *Industrial applications. The mycota (a comprehensive treatise on fungi as experimental systems for basic and applied research)*. Springer, Berlin
- Huerta B, Rodríguez-Mozaz S, Barceló D (2012) Pharmaceuticals in biota in the aquatic environment: analytical methods and environmental implications. *Anal Bioanal Chem* 404:2611–2624. <https://doi.org/10.1007/s00216-012-6144-y>
- Ikehata K, Jodeiri Naghashkar N, Gamal El-Din M (2006) Degradation of aqueous pharmaceuticals by ozonation and advanced oxidation processes: a review. *Ozone Sci Eng* 28:353–414. <https://doi.org/10.1080/01919510600985937>
- Jeong J, Jung J, Cooper WJ, Song W (2010) Degradation mechanisms and kinetic studies for the treatment of X-ray contrast media compounds by advanced oxidation/

- reduction processes. *Water Res* 44:4391–4398. <https://doi.org/10.1016/j.watres.2010.05.054>
- Kalsch W (1999) Biodegradation of the iodinated X-ray contrast media diatrizoate and iopromide. *Sci Total Environ* 225:143–153. [https://doi.org/10.1016/S0048-9697\(98\)00340-4](https://doi.org/10.1016/S0048-9697(98)00340-4)
- Kormos JL, Schulz M, Kohler HPE, Ternes TA (2010) Bio-transformation of selected iodinated X-ray contrast media and characterization of microbial transformation pathways. *Environ Sci Technol* 44:4998–5007. <https://doi.org/10.1021/es1007214>
- Kormos JL, Schulz M, Ternes TA (2011) Occurrence of iodinated X-ray contrast media and their biotransformation products in the urban water cycle. *Environ Sci Technol* 45:8723–8732. <https://doi.org/10.1021/es2018187>
- Küster A, Adler N (2014) Pharmaceuticals in the environment: scientific evidence of risks and its regulation. *Philos Trans R Soc Lond B Biol Sci* 369:20130587. <https://doi.org/10.1098/rstb.2013.0587>
- Liu Y, Hu J, Xu B, He J, Gao P, Liu K, Xue G, Ognier S (2013) Isolation and identification of an iopromide-degrading strain and its application in an A<sup>2</sup>/O system. *Bioresour Technol* 134:36–42. <https://doi.org/10.1016/j.biortech.2013.02.043>
- Machín-Ramírez C, Morales D, Martínez-Morales F, Okoh AI, Trejo-Hernandez MR (2010) Benzo[a]pyrene removal by axenic- and co-cultures of some bacterial and fungal strains. *Int Biodeterior Biodegrad* 64:538–544. <https://doi.org/10.1016/j.ibiod.2010.05.006>
- Markets and Markets Research Private Ltd (2020) Contrast media/contrast agent market by type (iodinated, gadolinium, barium, and microbubble), procedure (X-ray/CT, MRI, and ultrasound), application (radiology, interventional radiology, and interventional cardiology), regional forecast to 2024
- Matsushita T, Kobayashi N, Hashizuka M, Sakuma H, Kondo T, Matsui Y, Shirasaki N (2015) Changes in mutagenicity and acute toxicity of solutions of iodinated X-ray contrast media during chlorination. *Chemosphere* 135:101–107. <https://doi.org/10.1016/j.chemosphere.2015.03.082>
- Mikesková H, Novotný Č, Svobodová K (2012) Interspecific interactions in mixed microbial cultures in a biodegradation perspective. *Appl Microbiol Biotechnol* 95:861–870. <https://doi.org/10.1007/s00253-012-4234-6>
- Mruk B (2016) Renal safety of iodinated contrast media depending on their osmolarity—current outlooks. *Pol J Radiol* 81:157–165. <https://doi.org/10.12659/PJR.895406>
- Oliva G, Zarra T, Naddeo V, Munoz R, Lebrero R, Ángeles R, Belgiorno V (2018) Comparative analysis of AOPs and biological processes for the control of VOCs industrial emissions. In: Sironi S, Capelli L (eds) Proceedings of the chemical engineering transactions, vol 68, pp 451–456, AIDIC, Milan, Italy
- Pasternak JJ, Williamson EE (2012) Reactions of iodinated contrast agents: a primer for the non-radiologist. *JMCP* 87:390–402. <https://doi.org/10.1016/j.mayocp.2012.01.012>
- Polo AMS, López-Peñalver JJ, Sánchez-Polo M, Rivera-Utrilla J, Velo-Gala I, Salazar-Rábago JJ (2016) Oxidation of diatrizoate in aqueous phase by advanced oxidation processes based on solar radiation. *J Photochem Photobiol A Chem* 319–320:87–95. <https://doi.org/10.1016/j.jphotochem.2015.12.009>
- Radjenovic J, Petrovic M (2016) Sulfate-mediated electrooxidation of X-ray contrast media on boron-doped diamond anode. *Water Res* 94:128–135. <https://doi.org/10.1016/j.watres.2016.02.045>
- Rastogi T, Leder C, Kümmerer K (2014) Qualitative environmental risk assessment of photolytic transformation products of iodinated X-ray contrast agent diatrizoic acid. *Sci Total Environ* 482–483:378–388. <https://doi.org/10.1016/j.scitotenv.2014.02.139>
- Redeker M, Wick A, Meermann B, Ternes TA (2014) Removal of the iodinated X-ray contrast medium diatrizoate by anaerobic transformation. *Environ Sci Technol* 48:10145–10154. <https://doi.org/10.1021/es5014714>
- Rode U, Müller R (1998) Transformation of the ionic X-ray contrast agent diatrizoate and related triiodinated benzoates by *Trametes versicolor*. *Appl Environ Microbiol* 64:3114–3117
- Rodríguez-Couto S (2017) Industrial and environmental applications of white-rot fungi. *Mycosphere* 8:456–466. <https://doi.org/10.5943/mycosphere/8/3/7>
- Sacher F, Lange FT, Brauch HJ, Blankenhorn I (2001) Pharmaceuticals in groundwaters: analytical methods and results of a monitoring program in Baden-Württemberg, Germany. *J Chromatogr A* 938:199–210. [https://doi.org/10.1016/S0021-9673\(01\)01266-3](https://doi.org/10.1016/S0021-9673(01)01266-3)
- Schulz M, Löffler D, Wagner M, Ternes TA (2008) Transformation of the X-ray contrast medium iopromide in soil and biological wastewater treatment. *Environ Sci Technol* 42:7207–7217. <https://doi.org/10.1021/es800789r>
- Sheng S, Liu B, Hou X, Wu B, Yao F, Ding X, Huang L (2017) Aerobic biodegradation characteristic of different water-soluble azo dyes. *Int J Environ Res Public Health* 15:35. <https://doi.org/10.3390/ijerph15010035>
- Steger-Hartmann T, Lange R, Schweinfurth H (1999) Environmental risk assessment for the widely used iodinated X-ray contrast agent iopromide (Ultravist). *Ecotox Environ Safe* 42:274–281. <https://doi.org/10.1006/eesa.1998.1759>
- Thomsen HS (2011) Contrast media safety—an update. *Eur J Radiol* 80:77–82. <https://doi.org/10.1016/j.ejrad.2010.12.104>
- Thomsen HS, Dorph S (1993) High-osmolar and low-osmolar contrast media: an update on frequency of adverse drug reactions. *Acta Radiol* 34:205–209. <https://doi.org/10.3109/02841859309175354>
- Torresi E, Fowler SJ, Polesel F, Bester K, Andersen HR, Smets BF, Plósz BG, Christensson M (2016) Biofilm thickness influences biodiversity in nitrifying MBBRs—implications on micropollutant removal. *Environ Sci Technol* 50:9279–9288. <https://doi.org/10.1021/acs.est.6b02007>
- Velo-Gala I, López-Peñalver JJ, Sánchez-Polo M, Rivera-Utrilla J (2012) Ionic X-ray contrast media degradation in aqueous solution induced by gamma radiation. *Chem Eng J* 195–196:369–376. <https://doi.org/10.1016/j.cej.2012.04.046>
- Velo-Gala I, López-Peñalver JJ, Sánchez-Polo M, Rivera-Utrilla J (2014) Comparative study of oxidative degradation of sodium diatrizoate in aqueous solution by H<sub>2</sub>O<sub>2</sub>/Fe<sup>2+</sup>, H<sub>2</sub>O<sub>2</sub>/Fe<sup>3+</sup>, Fe(VI) and UV, H<sub>2</sub>O<sub>2</sub>/UV, K<sub>2</sub>S<sub>2</sub>O<sub>8</sub>/UV.

- Chem Eng J 241:504–512. <https://doi.org/10.1016/j.cej.2013.10.036>
- Wells G, Seidel FG, Sty JR, Swick HM (1988) Intrathecal administration of iopamidol in children: clinical and diagnostic results. *Pediatr Radiol* 18:190–193
- Wendel FM, Lutke Eversloh C, Machek EJ, Duirk SE, Plewa MJ, Richardson SD, Ternes TA (2014) Transformation of iopamidol during chlorination. *Environ Sci Technol* 48:12689–12697. <https://doi.org/10.1021/es503609s>
- Wendel FM, Ternes TA, Richardson SD, Duirk SE, Pals JA, Wagner ED, Plewa MJ (2016) Comparative toxicity of high-molecular weight iopamidol disinfection byproducts. *Environ Sci Technol Lett* 3:81–84. <https://doi.org/10.1021/acs.estlett.6b00037>
- Xu B, Gao P, Liu Z, Xue G, Liu Y, Wu F (2014) Influence of cosubstrates on iopromide degradation by *Pseudomonas* sp. I-24. *Water Air Soil Pollut* 225:1849. <https://doi.org/10.1007/s11270-013-1849-x>
- Ye T, Xu B, Wang Z, Zhang TY, Hu CY, Lin L, Xia SJ, Gao NY (2014) Comparison of iodinated trihalomethanes formation during aqueous chlor(am)ination of different iodinated X-ray contrast media compounds in the presence of natural organic matter. *Water Res* 66:390–398. <https://doi.org/10.1016/j.watres.2014.08.044>
- Zhang Y, Lv T, Carvalho PN, Arias CA, Chen Z, Brix H (2016) Removal of the pharmaceuticals ibuprofen and iohexol by four wetland plant species in hydroponic culture: plant uptake and microbial degradation. *Environ Sci Pollut Res* 23:2890–2898. <https://doi.org/10.1007/s11356-015-5552-x>
- Zhao C, Arroyo-mora LE, Decaprio AP et al (2014) Reductive and oxidative degradation of iopamidol, iodinated X-ray contrast media, by Fe(III)-oxalate under UV and visible light treatment. *Water Res* 67:144–153. <https://doi.org/10.1016/j.watres.2014.09.009>
- Zhou L, Ferronato C, Chovelon JM, Sleiman M, Richard C (2017) Investigations of diatrizoate degradation by photo-activated persulfate. *Chem Eng J* 311:28–36. <https://doi.org/10.1016/j.cej.2016.11.066>

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