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Review Article

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Occurrence of Paracetamol in Aquatic Environments and Transformation by Microorganisms: A Review

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Abstract

Paracetamol is a widely used for relieving pain and reducing fever worldwide as a non-prescription drug. It is one of the most pharmaceutical products often detected in sewage treatment plant effluents, surface water, and drinking water, so it has emerged as an imperative aquatic environmental pollutant, originating from pharmaceutical industries and human use. This review summarizes the pathways of paracetamol reach to the aquatic environments, its concentration, and proposed metabolic pathways of biotransformation. Paracetamol reaches water bodies via various paths.

The most important routes are the excretion by human beings and the industrial effluents originating from paracetamol active ingredients production. It was noticed that during the last years the paracetamol concentration increased in the aquatic environments, which indicates that it is not completely removed from wastewater by wastewater treatment plant (WWTP) as well as not entirely eliminated during ground water infiltration. Therefore, most of the paracetamol comes and leaches into the aquatic environment, groundwater and drinking water, through the discharges from this wastewater. On the other hand, biodegradation of paracetamol by microorganisms was used as a complement the method for transforming paracetamol into simpler constituents in the aquatic environment. The biodegradation mechanism varies from one microorganism to another. It was observed that the intermediate products are closely similar to each other. The comprehensive understanding of the metabolic pathways and enzyme systems involved in the utilization of paracetamol will be helpful for optimizing and allowing the rational design of biodegradation systems for paracetamol-contaminated wastewater, which expected to more efficient and will reduce the cost of treatment the pharmaceutical wastes in the aquatic environments.

Keywords: *Paracetamol Occurrence; Drinking Water; Waste water; Biotransformation; Microorganisms and Aquatic environment*

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Introduction

Paracetamol or acetaminophen is a widely used for relieving pain and reducing fever sold as over-the-counter (OTC) drug worldwide [1]. It is one of the most often detected pharmaceutical products in sewage treatment plant effluents, surface water, and drinking water [2]. Detection of this compound is greater in highly populated areas such as urban centers where drug usage is expected to reach elevated proportions [3]. The Frequent occurrence of paracetamol in aquatic environments and drinking water has raised a concern about their potential effects on the environment and human health [4].

Paracetamol consumption throughout the world has increased. It is ranked as one of the top three drugs prescribed in England and one of the top 200 prescriptions in the USA [5,6]. In Yemen, it is ranked as first of the top ten drugs produced by local industry and one of the top ten drugs imported [7]. Also, it was consumed as the second prescription during the year 2008 in Kuwait [8].

In the UK, about 3.2×10^9 tablets of paracetamol are consumed each year, which is an average of 55 tablets/person [9]. In the Nordic countries, the rates in some developed countries exceeded 20 g/person/year [10]. In 2002, the USA produced 3.6×10^9g of paracetamol [11]. It is easily accumulated in aquatic environment due to their high solubility and hydrophilicity, which have been detected in drinking water, surface water, and wastewater throughout the world [4].

The occurrence of this compound in the aquatic environment has stimulated investigations into the biodegradation and biotransformation by different microorganisms. Some microorganisms are capable of using paracetamol as carbon and energy source as well as capable of degrading and converting it to nontoxic compounds [4]. The strategies pathway for the paracetamol biotransformation by some microorganisms have been described [4,12,13].

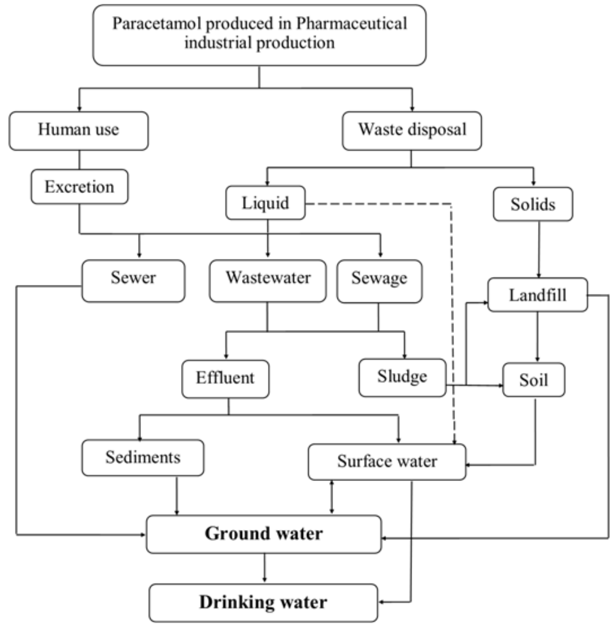
The production thousand tons of paracetamol annually have recently begun to receive a large amount of attention for its potential effects on the environment and human health. The increased use of this substance for long times will increase the presence in water sources. The aim of this work is to attempt to summarize the knowledge about the possible pathways of paracetamol reaches the aquatic environment from different sources. However, the presence of paracetamol concentration in drinking water, surface water, groundwater, wastewater, and sewage water around the world during the period from 1998 to 2016. The biotransformation mechanism for paracetamol with a different type of microorganisms.

Pathways of paracetamol reach the aquatic environment

According to previous studies about the possible sources and pathways of paracetamol reach the aquatic environment as shown in scheme (1). It is continuously introduced into the aquatic environment as a parent compound, metabolites or conjugate of both by pharmaceutical industrial effluents and human use [14,15]. These industries are releasing their effluents containing paracetamol substance originating from paracetamol active ingredients or formulation factories to wastewater. In addition, 58-68% of unchanged paracetamol is excreted from the human body during therapeutic use and disposed to sewage water [16,17].

The effluents containing paracetamol substance maybe discharge to the sewer, sewage treatment plant (STP), or wastewater treatment plant (WWTP). Paracetamol is known to be exhibited virtually no sorption and no retardation in aquifer sand which can eventually reach ground water as sources of drinking water via the sewer system [18].

Recent studies detected the paracetamol concentration in water discharged from STP and WWTP that is constantly released to surface water or be subjected to groundwater recharges [19]. Furthermore, the sludge from these treatment units which may contain paracetamol may be used as fertilizer in agricultural land. Over time, remains of this substance accumulate in the soil or drain into groundwater or surface water resources. The residues of paracetamol presence in water bodies especially drinking water reveal that STP and WTP are the major sources of entry of this substance into aquatic environment resulting from insufficient treatment the contaminated substance [20].



Scheme 1: *The possible sources and pathways for the occurrence of paracetamol residues in the aquatic environment.*

Paracetamol in aquatic environment

The occurrence of paracetamol in drinking waters

Paracetamol is a pollutant that has been found in the drinking water that could be used as drinking water sources in major cities such as Atlanta, Minneapolis, New York City, Oklahoma, and Minnesota City [21,22]. The paracetamol concentration was recorded between 0.0003-0.298 µg/L in drinking water. [23,24] .

The first detected of this substance in finished drinking water was observed in samples collected near Atlanta, Georgia [25]. In the USA, the paracetamol was reported in drinking water samples with level > 0.02 µg/L in Nevada [26], 0.12 µg/L and 0.0003 µg/L in source and finished drinking water, respectively [23] and 0.002 µg/L in 7% of drinking water samples [27].

Moreover, the paracetamol was recorded in France at 0.211 µg/L in a drinking water in Herault watershed [28], 0.210 µg/L in drinking water in Marseilles area [29], and 0.045 µg/L in finished drinking water [30]. Also, 0.298 µg/L and 0.017 µg/L of paracetamol were reported in source and finished drinking water, respectively, in Ontario, Canada [24]. Moreover, it was 0.260 µg/L and 0.010 µg/L recorded in source and finished drinking water, respectively, in Spain [31]. Table (1) summarizes the paracetamol concentrations detected in drinking water samples.

The occurrence of paracetamol in groundwater

The presence of paracetamol in groundwater is due to the infiltration of sewage effluent and surface water to the groundwater. During the soil passage, it is not efficiently sorbed to soil particles or biodegraded and still persistent [32].

Paracetamol has been detected in groundwater using for drinking water supplies in the USA. It was 0.036 µg/L and 6.5 µg/L detected, respectively, in public and private supplies wells in Massachusetts [33], 0.015 µg/L in groundwater wells in Nebraska [34], 0.16 µg/L in different groundwater samples [35], 0.38 µg/L in groundwater samples [36], 1.89 µg/L in samples of groundwater in California [37], and 0.12 µg/L in groundwater samples in Minnesota [38]. However, it was 0.034 µg/L detected in groundwater wells in Spain [39] and 0.010 µg/L (17%) in groundwater in Rhônee-Alpes, France [40]. Table (2) summarizes the occurrence of paracetamol concentrations detected in groundwater samples.

Country	Concentration (μg/L)	References
USA	> 0.02	26
	0.12–0.0003	23
	0.002	27
Canada	0.298–0.017	24
France	0.211	28
	0.210	29
	0.045	30
Spain	0.260 – 0.010	31

Table 1: *Paracetamol occurrence in the drinking water.*

Country	Concentration (μg/L)	References
USA	0.16	35
	0.015	34
	0.036 – 6.5	33
	0.12	38
	1.89	37
	0.38	36
Spain	0.034	39
France	0.010	40

Table 2: *Paracetamol occurrence in the groundwater.*

Paracetamol in surface waters

The presence of paracetamol in the surface waters such as lakes and rivers waters is due to the uncontrolled discharge of wastewater effluent to an environment containing this substance. It is one of the most frequently detected pharmaceutical products in approximately 75% of natural water such as rivers and lakes [23].

In the USA surface water, the paracetamol was detected at range 0.026 μg/L in Las Vegas Wash water, Nevada and 0.012 μg/L in Lake Mead water, Nevada and Arizona [41], between 1.95-10 μg/L in streams [42,43], 0.110 μg/L in surface water [44], 0.009 μg/L in surface water [45], 1.78 μg/L in surface water [46], 0.031 μg/L in New Jersey stream water [47], 0.117 μg/L in the Colorado River [48], 0.065 μg/L in the Mississippi River, New Orleans, Louisiana [49], and 0.012 μg/L in 13.3% of surface and subsurface samples of Tennessee River [50] (Figure 1).

However, in Germany, the paracetamol was found with concentration 0.065 μg/L in Elbe River water [51] and 1.99 μg/L in the Leine River [52]. In Spain surface water, it was 0.250 μg/L recorded in Ebro River basin water in Croatian [53], from 0.012 to 0.030 μg/L in three river waters (Ebre, Llobregat, and Ter) [54], 2.42 μg/L in Llobregat River [55], 0.043 μg/L in the Henares-Jarama-Tajo River in Madrid [56], 1.968 μg/L in the Mediterranean rivers in the Castellon province [57], and 0.021 μg/L in reservoir water, 0.243 μg/L in Onyar River, and 0.023 μg/L in Mediterranean Sea in Barcelona and Catalonia [58] (Figure 1).

In the UK, the paracetamol was found between 0.112-0.555 μg/L in surface water the South–East of England [59], 1.388 μg/L in River Taff, in Wales, and 0.058 μg/L in River Warta, Poland [60], and 1.534 μg/L in River Taff and 0.716 μg/L in River Ely in South Wales [61]. Also, it was ranged between 0.0041-0.073 μg/L in surface water in South Korea [2], 0.0348 μg/L in the Han River, North Korea [62], and 0.10 μg/L in the river water samples in Busan city, North Korea [63] (Figure 1).

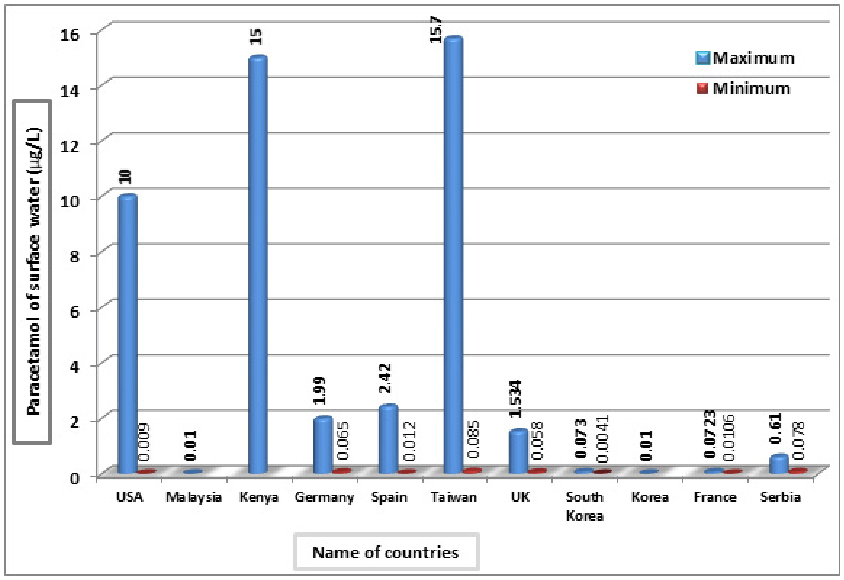


Figure 1: *Minimum and maximum concentrations of paracetamol occurrence in surface water worldwide.*

In France, the paracetamol was reported between 0.0106-0.0723 µg/L in surface water in Marseilles area [29], 0.071 µg/L in surface water [30], and 0.014 µg/L in surface water sampled from Rhônee-Alpes [40]. Also, it was ranged 0.078–0.610 µg/L in 15% of river water samples in Serbia [64], 3.35 µg/L in Sindian River, 15.7 µg/L in Dahan River, and 0.085 µg/L in Gaoping River in Taiwan [65], 0.01 µg/L in Langat River dam in Selangor, Malaysia [66], and up to 15 µg/L in the Nairobi River, Kenya [67] (Figure 1).

Paracetamol in wastewater

Paracetamol is one of the ubiquitous pharmaceuticals detected in wastewater at different concentrations throughout the world [68,69]. It was recorded between range 1.746-43.223 µg/L in WWTP influent samples and between 0.025-4.319 µg/L in 83% of WWTP effluent samples. Also, it was found between 13.874-177.674 µg/L in Ulleval university effluent samples and 5.421-1368.47 µg/L in Rikshospitalet wastewater in Oslo, Norway [68].

In the UK, the paracetamol concentration was reported from 5.529 to 69.57 µg/L in WWTP influent in Howdon [70], between 0.129-0.555 µg/L in WWTP effluent in England [59], 211.38 µg/L in influent and 11.733 µg/L in effluent of Cilfynydd WWTP as well as 178.116 µg/L in influent and 0.353 µg/L in effluent of Coslech WWTP in South Wales [61].

In Spain, the paracetamol was identified from 0.5-29 µg/L in hospital wastewater in Almerıa [71], from 0.130-26.09 µg/L in WWTP influent and 5.99 µg/L in effluent in Croatian [53], 0.123 µg/L in WWTP influent [72], 16.72 µg/L in WWTP influent and 0.338 µg/L in effluent in Barcelona and Catalonia [58], between 1.13-201 µg/L in WWTP influent in Castellon [69], and between 109.3-114.4 µg/L in hospital wastewater in Girona [73].

In the USA, the paracetamol was observed at level 1.06 µg/L in WWTP effluent [46], 0.96 µg/L in the Back River WWTP influent in Baltimore [74], 61 µg/L in WWTP influent and 0.86 µg/L in effluent in New York [75], 140 µg/L in hospital WWTP influent in San Marcos, Texas [76], 182-233 µg/L at five WWTPs influent in the Pacific Northwest [77], and 150.079 µg/L in effluents from fifty WWTPs [78]. Also, it was 1000 µg/L found in influent of WWTP in Wisconsin [79].

In the France, the paracetamol was up to 11.3 μg/L reported in a WWTP effluent [28], between 0.108–11.308 μg/L in WWTP effluent in Marseilles area [29], and 292 μg/L in WWTP influent [80]. Also, it was 23.3 μg/L recorded in wastewater influent in Sydney, Australia [81] and 1.7 μg/L in the WWTPs influent in Japan [82]. In South Korea, it was observed between 0–0.26 μg/L in influents and 0–0.16 μg/L in effluents of WWTP [83], between 0.0018–0.019 μg/L in WWTP effluents [2], and 21.95 μg/L in WWTP influent and 0.017 μg/L ultrafiltration effluents [84]. However, it was recorded with 20.6 μg/L in influent and 0.9 μg/L in effluent of WWTP as well as 9.3 μg/L in hospital WWTP influent and 3.6 μg/L effluent in Western Greece [85].

In North Korea, the paracetamol was 41.9 μg/L and 6.76 μg/L detected, respectively, in hospital WWTP influent and effluent. Also, it was 6.80 μg/L reported in the municipal WWTP influent [63] and 10.234 μg/L in influent of WWTP in Ulsan [86]. In Taiwan, it was recorded up to 186.5 μg/L in hospital wastewater influent and up to 417.5 μg/L in drug production facility wastewater influent [65], from 1.80–30.967 μg/L in six WWTPs effluents [87], and 2.695 μg/L in influent and 0.33 μg/L in effluent of WWTP [88].

In Italy, the paracetamol was 246 μg/L found in the raw WWTP influent [89] and from 1.4 to 5.9 μg/L in two hospital wastewater influents as well as 1.2 μg/L in WWTP influent and 0.058 μg/L in effluent [90]. However, it was 107 μg/L recorded in hospital wastewater influent in Switzerland [91], 150 μg/L in hospital wastewater in China [4], and up to 58.857 μg/L in hospital wastewater influent, 9.286 μg/L in WWTP influent and 0.106 μg/L in effluent in Coimbra, Portugal [92].

Furthermore, the paracetamol was recorded between 57.5-77.4 μg/L in the WWTP influent and 90.2 μg/L in the hospital wastewater influent in Québec, Canada [93]. In Kuwait, it was detected with highest concentration 2.086 μg/L in WWTP influent samples and 0.0521 μg/L in WWTP effluent in the 2011 year [8]. Also, it was 12 ug/L reported in hospital WWTP influent and 0.073 ug/L in WWTP effluent in Saudi Arabia [94]. Table (3) summarizes the paracetamol concentrations detected in influent (inf) and effluent (eff) of WWTP samples.

Country	Minimum (μg/L)	References	Maximum (μg/L)	References
Norway	1.746 (inf)	68	1368.47 (inf)	68
	0.025 (eff)	68	4.319 (eff)	68
UK	5.529 (inf)	70	211.38 (inf)	61
	0.129 (eff)	59	11.733 (eff)	61
Spain	0.123 (inf)	72	201 (inf)	69
	0.338 (eff)	58	5.99 (eff)	53
USA	0.96 (inf)	74	1000 (inf)	79
	0.86 (eff)	75	150.079 (eff)	78
France	0.108 (eff)	29	11.308 (eff)	29
			292 (inf)	80
South Korea	0.26 (inf)	83	21.95 (inf)	84
	0.0018 (eff)	2	0.16 (eff)	83
Western Greece	9.3 (inf)	85	20.6 (inf)	85
	0.9 (eff)	85	3.6 (eff)	85
North Korea	10.234 (inf)	86	41.9 (inf)	63
			6.76 (eff)	63
Taiwan	2.695 (inf)	88	417.5 (inf)	65
	0.33 (eff)	88	30.967 (eff)	87

Italy	1.2 (inf)	90	246 (inf)	89
	0.058 (eff)	90		
Portugal	9.286 (inf)	92	58.857 (inf)	92
	0.106 (eff)	92		
Canada	57.5 (inf)	93	90.2 (inf)	93
Kuwait	0.0521 (eff)	8	2.086 (inf)	8
Saudi Arabia	0.073 (eff)	94	12 (inf)	94
Japan	-	-	1.7 (inf)	82
Australia	-	-	23.3 (inf)	81
Switzerland	-	-	107 (inf)	91
China	-	-	150 (inf)	4

Table 3: *The minimum and maximum concentrations of influent and effluent paracetamol in WWTP.*

inf: inffluent, eff: effluent

Paracetamol in sewage waters

Paracetamol is reported as one of the most frequently detected pharmaceuticals in sewage treatment plant effluents [19]. The first occurrence of paracetamol was detected with concentration 6 μg/L in the STP effluent in German [95]. In Sydney, Australia, it was 148 μg/L recorded in STP influent [96]. Also, it was 1.9 μg/L found in the final effluents of eight STP in Atlantic Canada [97], 4.8 μg/L in STP influent and 1 μg/L in activated sludge effluent in the south of England, UK [98].

In Spain, the highest concentrations of paracetamol were found from 29–246 μg/L in STP influent and 4.3 μg/L in STP effluent in Almerıa [99], 37.458 μg/L in STP influent in Madrid [100], and 19.850 μg/L in STP influent in Catalonia [101]. Also, it was observed at level 56.9 μg/L in STP influent in Seoul, North Korea [62], 84 μg/L found in samples of STP influent situated in Stockholm, Sweden [102], and 0.07 μg/L in STP effluent in Selangor, Malaysia [66]. Table (4) summarizes the occurrence of paracetamol concentrations detected in sewage water samples.

Country	Concentration (μg/L)	References
German	6	95
Australia	148	96
Canada	1.9	97
UK	4.8	98
Sweden	84	102
Spain	37.458	100
	29–246	99
	4.3	
	19.850	101
Malaysia	0.07	66
Korea	56.9	62

Table 4: *Paracetamol occurrence in the sewage waters.*

Microbial degradation and transformation of paracetamol

The strategy for aromatic degradation includes hydroxylation and cleavage of the aromatic ring. Hydroxylation into the dihydroxylated intermediates is catalyzed by oxygenases belonging to three groups: hydroxylating dioxygenases, activated-ring monooxygenases, or nonactivated-ring monooxygenases. The main intermediates such as catechol, protocatechuic acid, hydroxyquinol, or gentisic acid are formed as a result of hydroxylation. These products are substrates for ring-cleaving dioxygenases [103,104].

Many of the researchers were focused on summarizing the studies on paracetamol biodegradation in the following aspects: paracetamol degrading bacteria, and proposed metabolic/biodegrading pathways in microorganisms, enzymes, and possible intermediates. It was recorded the ability of isolated Penicillium sp. to transform paracetamol to 4-aminophenol and acetate, maybe with the use of aryl acylamidase. 4-aminophenol is a dead-end metabolite [105] (Figure 2). Also, it was reported the ability of Rhodococcus strains to degrade paracetamol with three detectable metabolites: 4-aminophenol, catechol, and hydroquinone [106].

Further degradation of 1,4-hydroxybenzene could proceed in two ways. Hydroquinone may be directly cleaved by hydroquinone 1,2-dioxygenase with 4-hydroxymuconic semialdehyde as an aliphatic product [107]. Methylation of hydroquinone may further result in the mono and di O-methylated intermediates 4-methoxyphenol and 1, 4-dimethoxybenzene, as observed in the microbial transformation of paracetamol by two bacterial strains, Delftia tsuruhatensis and Pseudomonas aeruginosa [108]. Paracetamol was likely also metabolized via an amidohydrolase reaction and the cleavage of the bond between nitrogen and carbon from the carbonyl group would yield 4-aminophenol, from which nitrogen elimination followed by hydroxylation would lead to the formation of hydroquinone [109].

However, the Burkholderia sp. strain AK-4 was recorded to convert 4-aminophenol to 1,4-hydroxybenzene and further to 1,2,4-trihydroxybenzene. Then 1,2,4-trihydroxybenzene was cleaved by hydroxyhydroquinone 1,2-dioxygenase to maleylacetic acid, which is introduced to the basic metabolism [110,111] (Figure 2).

In further details, the conversion of paracetamol to hydroquinone was next transformed to an aliphatic product hexa-3-enedioic acid which seems that it was a product of aromatic ring fission or, if not, it that means some intermediate metabolites between aromatic and aliphatic compounds were passed over. Hexa-3-enedioic acid is similar to muconic acid-a product of ortho ring cleavage of catechol. Based on reported intermediates a primary pathway of paracetamol degradation could be proposed. The mechanism may be based on cutting off two carbon atoms in the form of formic acid [13] (Figure 2).

In addition, Akay and Tezel, (2016) reported that the *R. erythropolis* can convert paracetamol to phenols and organic acids by a series of hydroxylation reactions. During the biotransformation, paracetamol was initially converted to 4-aminophenol which was then transformed to hydroquinone by substitution of the amino group with hydroxyl. Hydroquinone then goes into ring fusion.

Furthermore, it was described the formation of glucoside conjugates with paracetamol by soil filamentous fungi via O- and N-linkages [113]. This is a similar way to the human detoxication routes of xenobiotics in phase II of detoxication [114].

Also, the degradation pathway of paracetamol in soil microorganisms was proposed and described. It was shown that in the first step, the aromatic ring of paracetamol is hydroxylated to 3-hydroxyparacetamol, oxygenated to N-acetyl-p-benzoquinone imine, or methylated to p-acetanisidide. N-acetyl-p-benzoquinone imine is then metabolized to 1,4-benzoquinone which is more stable and critical toxic metabolite. p-acetanisidide is transformed to 4-methoxyphenol and in the next step to the 1,4-dimethoxybenzene. The presence of 2-hexenoic acid in the soil extract suggests the cleavage of the aromatic ring of paracetamol [115].

In soil, monooxygenases such as flavin-containing hydroxylases are widely distributed among microorganisms and catalyze various oxidative reactions such as hydroxylation of phenols to catechols [116].

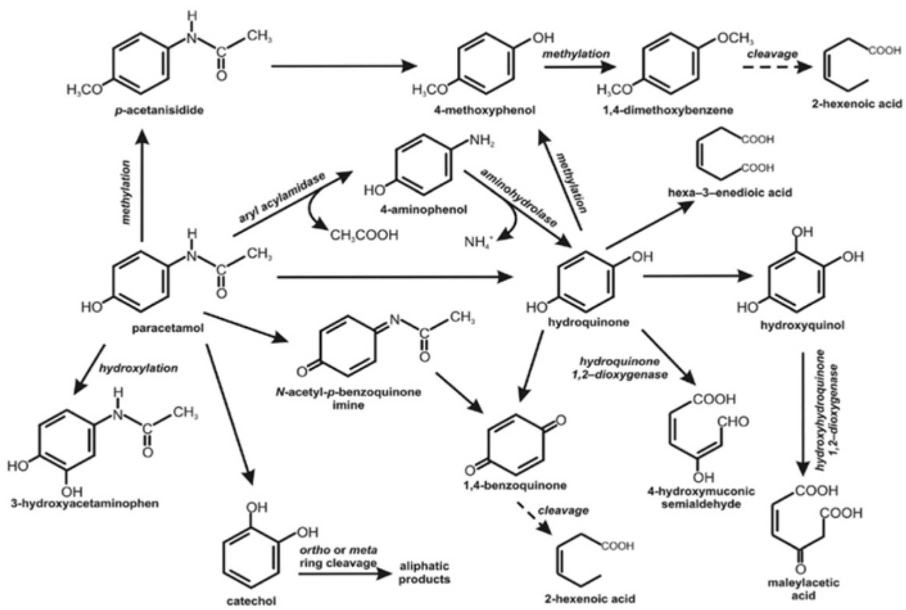


Figure 2: *Biotransformation of paracetamol pathways [117].*

Conclusion

The pharmaceutical industry holds a major role in polluting water resources. Paracetamol substance is constantly introduced into the aquatic environment by several discharges from manufacturing facilities, consumer use and disposal, and hospital waste. Nowadays the pharmaceutical industries are widely producing a thousand tons of paracetamol which are extensively using as non-prescription drugs worldwide. The wastewater containing a high concentration of paracetamol resulting from the production processes and excretion from human body during use is the main source for contaminating the aquatic environment. The detection of paracetamol in the surface water indicates that the WWTPs and STPs are insufficient to remove this substance completely from wastewater containing-paracetamol. Also, the existence of this substance in groundwater even at low concentration is the evidence that the paracetamol persists for degrading throughout the soil filtration. So, this substance is easily leaching into the aquatic environment as parent compound throughout the contaminated wastewater with paracetamol.

The high concentration of paracetamol occurrence in the aquatic environment is explained by the relationship between pharmaceutical consumption and WWTP efficiency. On the other hand, the microorganisms existing in the aquatic environment play an important role in degradation and transformation the paracetamol to nontoxic compounds. The biodegradation method for removing this substance have been investigated in advance. The enzymes produced from microorganisms are contributing to degrade and transform the paracetamol to intermediate compounds which are less harmful to aquatic environment. The development of innovative and cost-effective approaches is essential to ensure the complete elimination of paracetamol for the further protection of water quality and ecological health.

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