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Paracetamol - A Contaminant of High Concern: Existence in Environment and Adverse Effects

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Mini Review

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Abstract

Pharmaceuticals (analgesics and non-steroidal anti inflammatory drugs- NSAIDS) though, a major human scientific development, have undoubtedly lengthened life spans, cured millions from deadly diseases, and made life comfortable and free from pain. This very success has now led to their emergence as rapidly growing environmental pollutants and contaminants. Paracetamol (4'-hudroxyacetanilide, acetaminophen or N-acetyl-p-aminophenol) is amongst the most popular pain killers and widely used analgesic and antipyretic drug which is used for relieving pain and fever as a non prescription drug, worldwide. Such huge consumption all over the world can be expected to result in the contamination of the environment and threat to human health, since residual drugs after usage, easily accumulate in the environment especially aquatic environment through human excreta and industrial effluents produced from paracetamol active ingredients production. Its presence has been found in the environment which has been detected drinking water, waste water and sewage treatment plant effluents. Recent researches focus on adverse effects of paracetamol usage and health hazards in the form of increasing behavioural disorders in offspring.

Although chemical oxidation process is done for the treatment of waste water to remove paracetamol but severe reaction conditions, production of secondary pollutants as by products and huge operational expenses associated, leave no choice but to find other methods of treatment. Biodegradation of paracetamol by microorganisms is now being considered as an environment friendly alternative which has bearable cost. The widespread use of paracetamol and the scarcity of parallel and safe alternatives, its impact on the environment and on human health deserves further investigations and researches. The main aim of this review is develop comprehensive understanding on the percolation of paracetamol in environment through uncontrolled usage its toxic effects and proposed metabolic pathways of its biodegradation.

Keywords: Paracetamol; NSAIDS; Behavioural Disorders; Biodegradation; Aquatic Environment

Abbreviations: NSAID: Non-Steroidal Anti-Inflammatory Drug; COX: Cyclooxygenase; CNS: Central Nervous System; ADHD: Attention Deficit Hyperactivity Disorder; ASD: Autism Spectrum Disorder; PEC: Predicted Environmental Concentration; MEC: Measured Environmental Concentration; PNEC: Predicted No-Effect Concentrations.

Introduction

Pollutants and contaminants emerged from pharmaceuticals encompass synthetic chemicals that are present or transformed to new chemical compounds in environment across the globe. They are presently not

checked in the environment but pose a serious health threat to human and ecosystem as well as environmental damage. Pharmaceuticals (illicit and prescribed drugs) and their metabolic by products and their uncontrolled usage led to generation of water contaminants that affect the environment and human health [1-6]. Paracetamol is extensively used for reducing fever and as a pain killer for preventive and therapeutic purposes by all human beings including children and pregnant women [7]. Chemically it consists of a benzene ring substituted by one hydroxyl group and the nitrogen atom of an amide group at the para position. Due to its extensive usage paracetamol is one of the most easily detected pharmaceuticals in environment in different forms. Pharmaceuticals reach the environment in the form of expired medicines, unused medicines, in the form of excretory products or slightly metabolic form [8]. The consumption of paracetamol has increased many folds. In countries like U.K. and U.S.A. it is among the topmost prescribed drugs [9,10]. In spite of being used so extensively pharmaceuticals are still unregulated [11,12]. Their residues are considered as "compounds of emerging concern" in the environment because they cause considerable impact on human health and environment [13]. The pharmaceuticals as potential hazardous compounds for ecosystems were recently established [14,15]. The huge production of paracetamol on annual basis has drawn our attention to know its potential effects on the environment and human health (Figure 1).

Some Commonly used pharmaceuticals, their structure and application

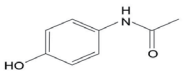
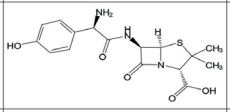
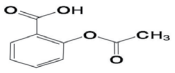
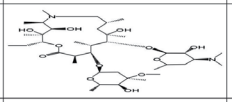
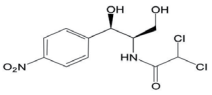
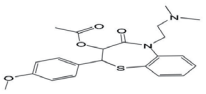
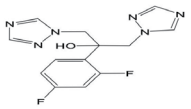
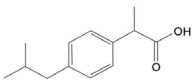
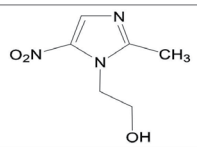
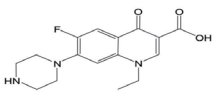
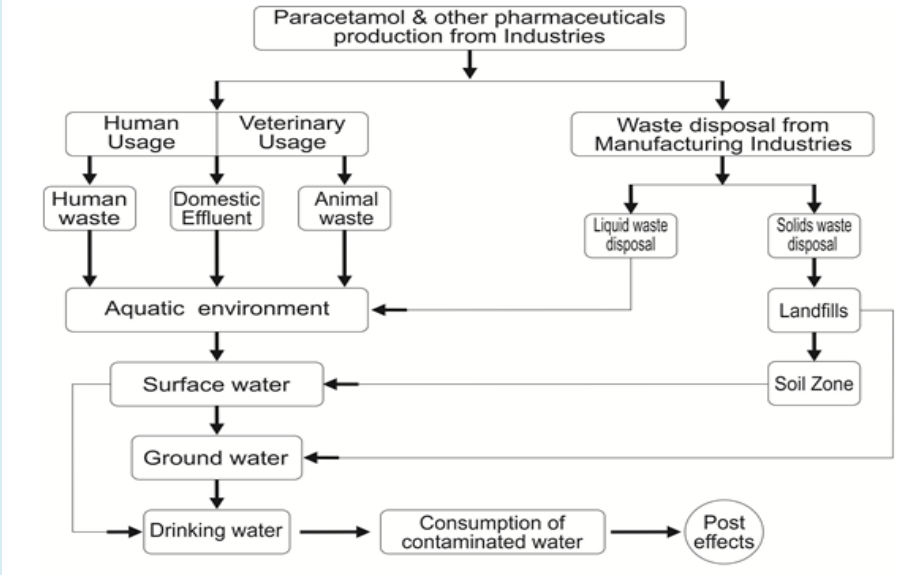
S.N	Pharmaceuticals	Chemical formula (Mol.wt.in g/l)	Predicted CEC (mg/L)	Structure	Theapeutic Application
1.	Acetaminophen (Paracetamol)	$C_8H_9NO_2$ (15/·165)	2·4E+07		Antipyretic / Analgesic Human and animal use
2.	Amoxicillin	$C_{16}H_{19}N_3O_5S$ (365.404)	7·4E+06		Antibiotic / Antibacterial/ B-lactums / Human applications
3.	Aspirin (Acetylsalicylic acid)	C_9 H_8O_4 (180.159)	3·4E+08		Analgesic/ Antipyritic Human and animal use
4.	Azithromycin	C_{38} $H_{72}N_2O_{12}$ (748.996)	1302		Antibiotic/ Antibacterial Human use
5.	Chloramphenicol	C_{11} $H_{12}Cl_2N_2O_5$ (323.126)	8·1E+06		Antibiotic/ Antibacterial/ Broad spectrum antibiotic/ Human use
6.	Diltiazem	$C_{22}H_{26}N_2O_4S$ (414.52)	27884		Calcium channel blocker/ Antihypertensive Human use
7.	Fluconazole	$C_{13}H_{12}F_2N_6O$ (306.277)	5·0E+06		Antifungal
8.	Ibuprofen	$C_{13}H_{18}O_2$ (206.285)	194711		NSAIDs
9.	Metronidazole	$C_6H_9N_3O_3$ (171.156)	2·3E+07		Antibiotic/ Aniprotozoal/ Nitromidozole
10.	Norfloxacin	$C_{16}H_{18}FN_3O_3$ (319.336)	6·4E+06		Antibiotic/ Fluoroquinolone Human applications

Figure1: Some commonly used pharmaceuticals worldwide [16,17].

The main aim of this review was to summarize the latest knowledge about occurrence, toxicity, degradation pathways and enzymes involved in biodegradation of paracetamol as one of the most emerging contaminants. The review presents concrete analysis of presence of paracetamol in the environment, its toxic effects on human health and environment and consequent actions to decrease its presence as contaminant from the environment mainly by reduction of its release and efficient biodegradation.

Sources and Pathways How Paracetamol and Other Pharmaceuticals Reach in the Environment

Pharmaceuticals reach the environment mainly through the domestic wastewater, hospital effluents, industrial wastewater from pharmaceuticals production, run-off from aquacultures and concentrated animals feeding operations, fish farming as well as a rural run-off and manure, disposal and discharges from pharmaceutical production industries [18-22]. Prevalent occurrence of paracetamol and its degradation product (4-aminophenol) in the environment is partly associated with their use for manufacturing of azo dyes and photographic materials [23]. It is continuously introduced in to the environment as a parent compound and in the form of its metabolic products by human and veterinary usage, effluents and waste disposal from pharmaceutical industries [2,24]. The continuously increasing concentrations of paracetamol and other emerging pharmaceutical as contaminants may result in the occurrence of toxic phenomena in non-target species present in aquatic environments. According to a recent research the extremely high dispersion of paracetamol in environmental its ecotoxicological assessment should be a priority for all. Due to conservative nature of physiological processes and similarity of target molecules some consequences may be seen in the human beings and aquatic environment due to continuous contamination of the environment with pharmaceuticals [25]. Paracetamol is not highly persistent and can be found in the environment in high concentrations and can cause negative effects on ecology due to huge introduction into the environment which can strongly affect its high transformation rates [26]. Paracetamol has recently been listed in the list of the compounds relevant for India (a developing country) as emerging contaminants which are detected in water of a developing country examined by considering the data related to pharmaceutical consumption data [27]. The possible pathways how pharmaceuticals reach in the environment have been developed from various researches and literature available is mentioned in Scheme 1 [28].



Scheme 1: The possible pathways of how pharmaceuticals reach in the environment.

Occurrence of Paracetamol in the aquatic environment (in micrograms per litre) [29].

Surface Water	Reference	Finished Water	Reference
0.11	[30]	0-0.16	[35]
0.52-0.56	[31]	0.048-0.418	[36]
0.007-0.066	[32]	0-5.99	[34]
0-0.026	[33]	0.079-0.22	[31]
0-0.25	[34]	1.9	[37]

Pharmaceuticals have been reported in aquatic environments remarkably in the form of groundwater, drinking water, drinking water treatment plants [38-39] affecting human health which is a matter of major concern. Moreover, paracetamol easily accumulates in the aquatic environment and it is known to exhibit virtually no sorption nor retardation in aquifer sand studies [40].

Environmental Toxicity and health risks (challenges and threats)

Paracetamol is a non-steroidal anti-inflammatory drug (NSAID) which has a different mechanism of action from other NSAIDs. Its mode of action is not clearly understood, but it appears to inhibit cyclooxygenase (COX) in the brain selectively to treat fever and pain. It may also inhibit prostaglandin synthesis in the central nervous system (CNS). Acetaminophen directly acts on the hypothalamus producing an antipyretic effect [41]. The exposure to paracetamol at the concentration of 66mg/kg body weight has undesirable effects on living organisms like alterations in biochemistry and histopathology in the liver of rats [42] and 5 and 15mg/kg body weight exposure to acetaminophen in the early stages of development affects the neurotransmission associated with the medulla oblongata [43] or it can directly affect the spinal cord [44]. There have been many reports in the past which claim that the hepatotoxicity of paracetamol is highly increased in chronic alcoholics, and such individuals' carry an increased risk of severe and fatal liver damage after acute over dosage [45-55]. The serious liver damage may also occur with 'therapeutic' use of this drug [56-61]. Until recently, usage of paracetamol was considered safe in pregnancy. But now it has become controversial that use of this medicine may create future impacts on the offspring if used by the mother during pregnancy. According to a latest literature review the diverse epidemiological studies connect the exposure of paracetamol to offspring having behavioural disorders like ADHD (attention deficit hyperactivity disorder) and ASD (autism spectrum disorder) though there is little evidence to support the association of paracetamol with functioning of brain if used during pregnancy [62]. According to a report the ecological risk assessment calculated as the ratio between the predicted environmental concentration (PEC) and measured environmental concentration (MEC) to the predicted no-effect concentrations (PNEC) of the pharmaceuticals, which is basically related to the harmful dose of various pharmaceuticals to different species living in the aquatic environments [63].

Biotransformation or Biodegradation

Micropollutants being extremely diversified in structure, their unsaturated/saturated character, the presence of various functional groups (e.g., halogen, sulfate), and linear or branched structure, there is no specific method used for the sewage treatment for their utilization. However some advances technologies for the treatment of wastewater containing paracetamol are advanced oxidation processes and chemical oxidation processes such as TiO2 photocatalysis [64,65], Ozonation technique [66], solar photoelectron-Fenton oxidation [67] etc. High operational cost, severe reaction conditions and generation of by-products as secondary pollutants which are really difficult to remove finally from the environment make these oxidation processes not a desirable and convenient choice [68]. Due to the lack of the optimal treatment techniques many pollutants are released in their parent form as more stable metabolites to the environment [69]. This could result in the accumulation of these metabolites in tropic chains and create long-term adverse effects on aquatic organism [70].Therefore, degradation of these micro pollutants especially paracetamol can be considered as an alternative being environment friendly and cost effective in nature. Microorganisms play a significant role in biological decomposition of hazardous compounds present in the environment. However, not much information is available on this aspect. During the past decades researches were focused on identification of metabolic intermediates and pathways during bacterial degradation of paracetamol (in animals) in laboratory. In most of the cases paracetamol was biodegraded in to hydroquinone via 4-aminophenol, in different animals. Furthermore, paracetamol can be converted to phenols and organic acids by *R. erythropolis* by a series of hydroxylation reactions [71]. However, other pathways where paracetamol is degraded into pyrocatechol have also been reported [72].

According to a report species of *Pseudomonas* degraded 96% of 1500mg/L paracetamol for the incubation of 12hrs [73] and it is recognised for its ability to degrade aromatic compounds of environment concern.

Conclusion

Despite being used from decades extensively, paracetamol has unintended presence in the environment which must be recognised as an emerging organic micro pollutant and threat to global health. It is constantly introduced in the environment in the form of waste disposal and effluents from manufacturing industries, human and animal waste and several metabolic by products. Therefore the presence of organic micro pollutants in different environmental matrices needs more research, planning of mitigation strategies, and implementation of strategic measures to detect and remove it in environment friendly manner. The mechanisms of biological degradation and their genetic bases are still poorly understood. Latest researches should be focused on development of effective eco-friendly techniques like biotransformation and biodegradation which would be having high removal rate and cost efficiency. Microorganisms produce those enzymes which effectively degrade and transform the metabolic intermediates and by products of paracetamol in to non-toxic components.

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