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Research Paper

Emerging contaminants as unintentional substances in paper and board: A case of unexpected pharmaceuticals detection in the paper recycling chain

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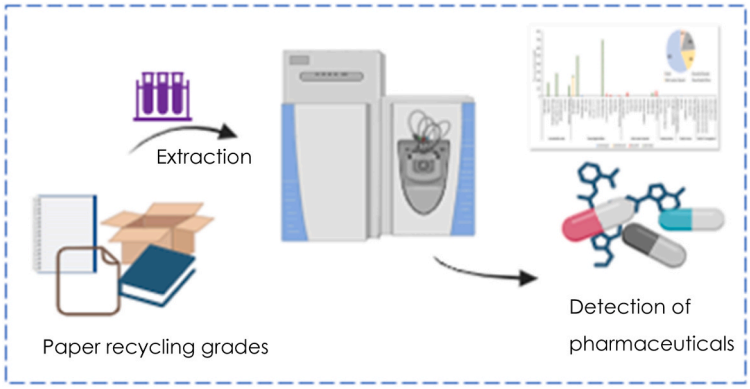
HIGHLIGHTS

- The first reported occurrence of pharmaceuticals contamination in paper samples.
- Targeted and suspect screening of various paper grades was performed.
- Sensitive analytical method developed using UHPLC- Q Orbitrap.
- Reveals the propagation of emerging contaminants beyond environmental matrices.
- Consumer usage and waste management protocols contributed to pharmaceutical occurrence.

GRAPHICAL ABSTRACT



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ABSTRACT

The contamination of paper products by various chemicals has been reported on a global level, but to date, no published research has investigated pharmaceutical contamination of paper-based products. In this study, pharmaceutical analysis was conducted on 42 samples collected from various points of the recycled paper value chain in Cape Town, South Africa, which included the various grades that may be included in the manufacturing of recycled paperboard. The analysis was achieved by ultrasonic-assisted extraction of paper samples before detection by UHPLC-Q Orbitrap. Quantification limits ranged from 1.15 pg/g for ketoprofen to 46.07 pg/g for methocarbamol. Pharmaceuticals identified in newspaper samples were dexamethasone, ketoprofen, and 17β-estradiol. The latter was also detected in paper shopping bags (up to 697.49 ng/g), infant bathtub packaging (280.62 ng/g), battery packaging (137.43 ng/g), and an egg carton (170.47 ng/g). Carbamazepine was also prominent with its concentration reaching 13.02 ng/g in a vegetable box. Suspect screening tentatively identified 14 additional pharmaceuticals in paper samples, with minocycline, prazepam, and anabolic steroids appearing more prominently. This pioneering study indicated that unintentional pharmaceutical exposure had expanded beyond environmental media to consumer products.

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1. Introduction

Pharmaceuticals have been detected in freshwater bodies [1] reclaimed wastewater [2], sewage sludge, soils [3], marine organisms [4], food products [5] as well as in plants and animals due to their uptake from the contaminated environment [6]. The presence of pharmaceuticals in the environment has been attributed to poor sanitation [7], wastewater treatment plants (WWTPs) [8], inaccessibility to modern ablution facilities, and improper disposal of expired or unused medications [7]. On a global level, the complete elimination of pharmaceutically active compounds and their metabolites by WWTPs does not occur [5,9]. For this reason, pharmaceuticals are considered emerging environmental pollutants [2,5]. In South Africa, different therapeutic classes of pharmaceuticals which include nonsteroidal anti-inflammatory drugs (NSAIDs), antiretroviral drugs, antibiotics, β-blockers, antidiabetics, lipid regulators, antidepressants, antipsychotics, muscle relaxants and anti-epileptics have been identified in the environment [1]. Unintentional exposure to pharmaceuticals is associated with adverse environmental and human effects. For instance, the presence of antibiotics in the environment has been linked to altered bacterial compositions in stable ecosystems and to antibiotic-resistant bacteria [10]. Antiepileptics have been shown to modify electrical activities in the neurons[11] while NSAIDs reportedly inhibit brain development in foetus [5].

Paper recycling involves extensive water use for pulping, fibre property development, dilution of pulp, paper web formation, and steam generation; often in closed-water systems [12]. Since pharmaceutically active compounds have been identified as water contaminants [1–3], pharmaceuticals may thereby be introduced to the fibre lattice during the paperboard manufacturing process. Paper-based materials are also often used as secondary packaging for pharmaceutical products [13], which could further promote pharmaceutical exposure opportunities. The circular nature of paper recycling [14] in itself means that pharmaceuticals may accumulate and propagate in the paper recycling chain; exacerbated by the sorting and collection protocols employed. The mingling of paper with other waste products during disposal, collecting, and sorting as well as consumer contact and usage has been shown to introduce contaminants [15,16] and may thus also lead to pharmaceutical contamination. Moreover, the interaction of post-consumer paper with the environmental media when disposed of in soil, water, and vegetation may inadvertently provide other opportunities for pharmaceutical contamination of waste paper intended for recycling; where no mechanisms are currently used to actively remove such compounds. In South Africa, the paper recycling chain includes paper recovered from unsorted domestic waste as well as paper collected at kerbsides, solid waste disposal sites, and landfills by informal waste collectors commonly referred to as waste pickers. This results in increased exposure opportunities to water, soil, plants, and leachates. Since pharmaceuticals are ubiquitous in environmental media [17] exposure to pharmaceuticals is highly probable in the paper recycling chain.

Cellulose fibres such as those present in paper pulps are hydrophilic [18] and are referred to as hygroscopic material with the ability to absorb, or desorb, water vapour in the air and liquid water from their surroundings [19]. Paper is highly sensitive to gases and liquids which can diffuse through the highly porous material [20] increasing opportunities for pharmaceutical contamination. To minimise and improve general barrier properties, non-cellulosic polymers, waxes, and aluminium are often added to the paper during manufacturing [20]. In more recent years, biopolymers (such as polycaprolactone and polylactic acids) and hydrocolloids (including starch, chitosan, and cellulose derivatives) [20–22] have been used to improve the functional performance of paper products, to introduce hydrophobicity and to reduce the introduction of contaminants [23] This thereby means that different paper products may adsorb or absorb chemical compounds differently depending on the barrier coating, retention aids and wet-strength additives used.

The contamination of paper products by various chemical compounds such as phthalates, benzophenone, phenols, and mineral oil has been reported [24–30], but to date, no published research has investigated pharmaceutical contamination of paper products. The lack of literature on the occurrence of pharmaceuticals in paper-based goods meant that the pharmaceuticals of interest were selected based on recent works on pharmaceuticals in water bodies and reported usage patterns of pharmaceuticals in South Africa. To this end, an anti-epileptic drug (carbamazepine), NSAID (ketoprofen), corticosteroid (dexamethasone), steroid hormone (17β-estradiol), antiretroviral (nevirapine), antidepressant (venlafaxine), muscle relaxant (methocarbamol) and cardiac stimulant (etilefrine) were selected as representative analytes of the main therapeutic classes of pharmaceuticals found in the South African environment [31–34]. The occurrence of these pharmaceuticals was investigated at key stages of the paper recycling chain; pre-consumer, retail, and post-consumer. The pre-consumer samples comprised of paperboard prior to exposure to consumers (with a recycled fibre component) whilst retail samples consisted of samples that had been packed and distributed to grocery stores. The post-consumer samples included the various grades of paper grades used to manufacture recycled paperboards, such as newspapers, magazines, and office paper. These were used post-consumer samples. The commingled paper collected for recycling in South Africa, like many developing countries such as Brazil, Argentina, Nigeria, and India [35] includes paper recovered by informal waste pickers. Waste pickers collect waste from kerbsides, solid waste disposal sites, and landfills. Poorly managed waste systems have resulted in unrestricted waste collection and inappropriate disposal of waste [36]. A portion of this wastepaper, destined for end-of-life disposal or incineration, ends up at recycling facilities along with waste paper collected from households, retailers, schools, businesses, and various industries before being manufactured into recycled paperboard. The analysis was achieved by ultrasonic-assisted extraction before detection by ultra high performance liquid chromatography – high resolution mass spectrometry (UHPLC-HRMS) Q Orbitrap.

2. Materials and methods

2.1. Chemicals and preparation of pharmaceutical standards

The analytical standards consisted of carbamazepine, dexamethasone, nevirapine, venlafaxine, methocarbamol, etilefrine, ketoprofen, and 17β-estradiol (Merck, Johannesburg, South Africa) as shown in Table 1. These were made up in LC-MS grade methanol (Merck, Johannesburg, South Africa) at a concentration range of 10 - 500 μg/L. Other solvents used in the study were ethanol (Merck, Johannesburg, South Africa) and water (Merck, Johannesburg, South Africa).

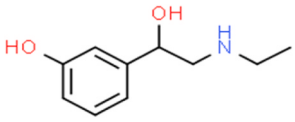
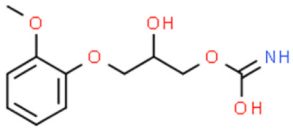
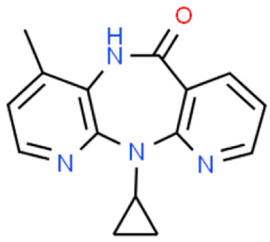
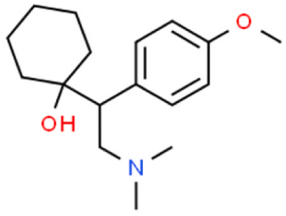
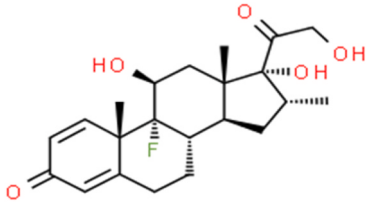
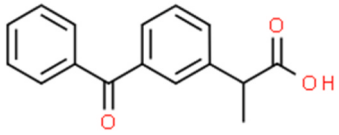
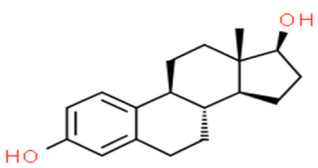
2.2Sampling

A total of 42 paper and board samples were collected at solid waste sites, recycling facilities, retail stores, informal waste pickers, and household waste in Cape Town, South Africa (Fig. 1) and consisted of various grades in the paper recycling chain that go into the manufacture of recycled boards. Pre-consumer samples were sourced from various South African corrugators and paper mills situated outside the Cape Town district, with the samples collected from the paper machine, wrapped in foil, and dispatched. The retail samples were collected from South African grocery stores. The pre-consumer and retail samples consisted only of the board, whilst the post-consumer samples consisted of the paper grades typically used in the manufacture of recycled boards. These samples consisted of cartonboard, newsprint, corrugated board, office paper, and magazines.

2.3Sample preparation

A sample of 1 g shredded paper was placed in a 20 mL solvent mixture consisting of water: ethanol: and methanol (2:1:1) inside a 60 mL glass vial and vortexed for 2 min. This was followed with ultrasonic-assisted extraction (UAE) at 60 ℃ for 2 h in a sonic bath (Power Sonic 405, United Scientific, Cape Town). The extraction process strategically aimed for the release of target pharmaceuticals from the paper-based samples into an aqueous medium. The addition of methanol and ethanol was done to improve extraction efficiency as done

Table 1
Pharmaceutical standards.

Pharmaceutical	Chemical Formula	Chemical Structure	CAS #	Water solubility (mg/L)	LogP	LogD (pH 7.4)	Boiling Point (℃)
Etilefrine	$C_{10}H_{15}NO_2$		709-55-7	18.9	0.5	-1.61	352
Methocarbamol	$C_{11}H_{15}NO_5$		532-03-6	29.9	0.61	-2.07	418
Nevirapine	$C_{15}H_{14}N_4O$		129618-40-2	100	2.5	2.10	415
Venlafaxine	$C_{17}H_{27}NO_2$		93413-69-5	572×10^3	3.2	1.43	398
Carbamazepine	$C_{15}H_{12}N_2O$		298-46-4	35.4	2.77	2.28	411
Dexamethasone	$C_{22}H_{29}FO_5$		50-02-2	89	1.87	1.92	568
ketoprofen	$C_{16}H_{14}O_3$		22071-15-4	51	3.1	0.06	431
17β-estradiol	$C_{18}H_{24}O_2$		50-28-2	3.9	4	3.62	446

elsewhere [38] whilst remaining compatible with the UHPLC- Q Orbitrap solvent system. The selection of 60 ℃ was based on the boiling temperature of the solvents, to closely match typical pulping temperature [39] and to improve extraction that would otherwise be achieved at lower temperatures [40]. The boiling points of the target compounds were all above 350 ℃ (Table 1) and so were not expected to volatilise. The resulting supernatants were filtered into glass vials with a 0.22 μm regenerated cellulose filter (Stargate Scientific, Johannesburg, South Africa) before analysis using UHPLC-Q Orbitrap.

2.4. UHPLC-Q Orbitrap

UHPLC-HRMS analysis was performed using a Thermo Scientific Vanquish UHPLC^{+} Q Exactive Focus Orbitrap (Anatech, Cape Town, South Africa). Chromatographic separation was achieved using a Hypersil Gold aQ 100 mm x 2.1 mm x 1.9 μm column (Anatech, Cape Town, South Africa) at a column compartment temperature of 30 °C and autosampler temperature of 10 °C. The instrument method developed was guided by compound chemical characteristics and instrument capabilities [41–44] with the final optimised conditions consisting of solvent A as 0.1 % formic acid in water (Merck, Johannesburg, South Africa) with 5 mM ammonium formate (Merck, Johannesburg, South Africa) and solvent B as 0.1 % formic acid in methanol with 5 mM ammonium formate. The gradient method was initiated at 30 % solvent B at 0.3 mL/min (hold 1 min) before increasing to 100 % B with a curve set at 2 until 15 min. The flow rate was increased to 0.35 mL/min for 4 min before returning to 30 % solvent B and 0.3 mL/min. A 10 μL injection volume was used. Tandem mass spectrometry was coupled to a heated electron spray ionisation spray in positive mode with the sheath gas flow rate at 40 aU, the aux gas flow rate at 10 aU, spray voltage at 3.20 kV, S-lens RF level at 55.0, 300 °C capillary temperature and 400 °C aux gas heater temperature. The full scan acquisition range was 83.4 to

Fig. 1. Sample overview in Cape Town (Western Cape province, South Africa). Adapted from [37].

1250 m/z at a resolution of 70 000, and data-dependent acquisition (dd-MS^2) in discovery at a resolution of 35 000. Stepped collision energy was selected at 15 and 30 eV with the AGC target set at 2E+ 04. The accurate mass analysis and retention times for the compounds were determined by Eq. (1).

$$Mass\ tolerance(ppm) = |\frac{Theoretical\ mass\ expected(m/z) - Mass\ Observed(m/z)}{Theoretical\ mass\ expected(m/z)}| \times 10^6 \quad (1)$$

For HRMS, a mass tolerance < 5 ppm indicates accurate mass detection [45].

2.5. Quality assurance

To evaluate the external calibration curves, the coefficient of determination (R^2) was determined as the indicator of linearity. The limit of detection (LOD) and limit of quantification (LOQ), which were taken as the sensitivity indicators, were measured at signal-to-noise of 3 and 10, respectively at 10 µg/L. Virgin, unconverted, unprinted paperboard samples were used to evaluate the method performance by spiking the samples at two different concentrations in triplicate. Spiking was performed on virgin samples using standards made up in methanol which were allowed to dry for approximately 3 h at 21 °C prior to the extraction procedure. The relative recovery and %RSD were used to evaluate the accuracy and precision of the method.

2.6. Data analysis

Instrument data acquisition and analysis were performed using Thermo Scientific Xcalibur and TraceFinder 5.0. TraceFinder 5.0 was used for suspect screening where an unknown analysis method was developed for a minimum peak width of 0.21 min, maximum peak width of 0.74 min, and Retention Time window set at 35 s with alignment and gap filling selected for exhaustive searching. The mass tolerance for the screening was set at 10 ppm on the full scan using the National Institute of Standards and Technology (NIST) 2020 library. The match factor gave an indication of the similarity of the unknown spectrum to the library spectrum at a scale of 0–1000 with the highest possible score of a perfect match being 999. General guidelines from NIST indicated that a match factor > 900 was considered an excellent match, 800–900 a good match, and 700–800 a fair match. In the reverse match the peaks of the unknown's spectrum that are not in the library's known reference spectrum were ignored. The threshold for positive identification was based on match factors and accurate mass tolerance where the similarity index (SI) was above 750 and the reverse similarity index (RSI) above 800.

3. Results and discussion

3.1. Method validation

Acceptable mass accuracy was achieved, as shown in Table 2, with mass tolerance < 5 ppm for all target compounds under investigation at the retention times stated using the confirmatory ions listed. The chromatogram obtained for the separation of target compounds is shown in Fig. 2.

Method validation parameters were determined and are listed in Table 3. The R^2 of the calibration curves ranged from 0.97 to 0.99 indicating good overall linearity of the target compounds. The LODs were found to range from 1.15 pg/g for ketoprofen to 46.07 pg/g for methocarbamol whilst the LOQs ranged from 3.84 pg/g for ketoprofen to 153.57 pg/g for methocarbamol. The recoveries of the paperboard were performed by spiking samples at 50 and 100 ng/g with the lowest recovery obtained for nevirapine being 52.63 % at 50 ng/g and the highest for dexamethasone at 95.42 % for 100 ng/g. The reduced recovery of nevirapine at the lower spiking level may have likely been influenced by poorer ionisation efficiency of the four nitrogen (bond acceptor) - containing nevirapine (Table 1) in the pH 2.7–4.7 buffered mobile phase [46].

The differences in the recoveries for the eight target compounds were likely due to differences in the solubility of the pharmaceuticals in the extraction solvent, the chemical structures, and the logP values (Table 1). The logP indicated how readily the pharmaceutical would partition between an aqueous and an organic phase (Eq. (1)) [47]. Better recovery was obtained from the pharmaceuticals having higher log P values. LogD, as defined in Eq. (2), is the measure of lipophilicity of ionisable compounds [48] and is often used to evaluate pharmaceutical partitioning in water [48–50].

$$LogP = Log\frac{[neutral\ compound]_{oct.}}{[neutral\ compound]_{aq.}} \quad (1)$$

where [neutral compound] is the concentration of the compound in its neutral form at pH = 7 as a ratio in octanol (oct.) to aqueous (aq.) medium.

$$LogD = Log\frac{[neutral\ and\ ionised\ compound]_{oct}}{[neutral\ and\ ionised\ compound]_{aq}} \quad (2)$$

where [neutral and ionised compound] is the sum of the neutral and ionised concentration of the compound as a function of pH as a ratio in octanol (oct.) to aqueous (aq.) medium.

From Table 1, it was evident that for the 100 ng/g spiking

Table 2
Pharmaceutical accurate mass detection.

Compound	Confirmatory Ion (m/z)	Monoisotopic Mass (amu)	$[M+H]^+$ Theoretical Mass expected	Observed Mass (m/z)	Mass tolerance (ppm)
Etilefrine	164.1069	181.1103	182.1181	182.1176	2.77
Methocarbamol	118.0500	241.0950	242.1028	242.1023	2.23
Nevirapine	198.0147	266.1168	267.1246	267.1241	1.82
Venlafaxine	121.0649	277.2042	278.2120	278.2116	1.50
Carbamazepine	194.1175	236.0950	237.1028	237.1021	2.87
Dexamethasone	237.1272	392.1999	393.2077	393.2074	0.80
Ketoprofen	209.0961	254.0943	255.1021	255.1015	2.35
17β-estradiol	255.1372	272.1776	273.1854	273.1859	1.83

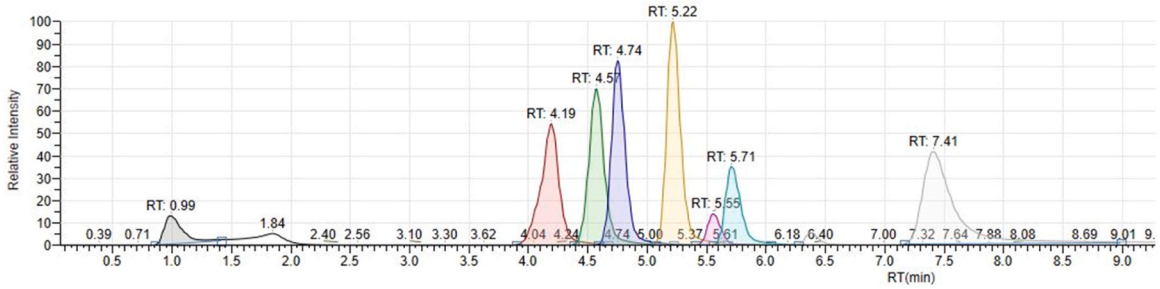


Fig. 2. A chromatogram demonstrating the separation of eight target pharmaceuticals, where RT represents the retention time (min) of each compound, with the elution order of etilefrine, methocarbamol, nevirapine, venlafaxine, carbamazepine, dexamethasone, ketoprofen, and 17β-estradiol at RT: 0.99, 4.19, 4.57, 4.74, 5.22, 5.55, 5.70, 7.41, respectively.

Table 3
Method validation.

Compound	R^2	LOD± % RSD (pg/g)	LOQ± % RSD (pg/g)	% Recovery ± %RSD (n = 3)	
				Paperboard spiking level (ng/g)	
				50	100
Etilefrine	0.9921	14.44 ± 11.8	48.15 ± 11.8	86.05 ± 1.5	68.19 ± 9.0
Methocarbamol	0.9952	46.07 ± 9.5	153.57 ± 9.6	73.99 ± 4.9	74.89 ± 8.4
Nevirapine	0.9704	2.21 ± 12.3	7.37 ± 12.3	52.63 ± 2.2	87.85 ± 1.1
Venlafaxine	0.9988	3.27 ± 0.4	10.90 ± 0.4	88.49 ± 6.9	87.55 ± 2.7
Carbamazepine	0.9884	3.49 ± 4.3	11.65 ± 4.3	72.50 ± 5.8	91.01 ± 4.9
Dexamethasone	0.9988	31.80 ± 7.1	105.99 ± 7.1	83.15 ± 1.9	95.42 ± 2.8
Ketoprofen	0.9977	1.15 ± 6.8	3.84 ± 6.8	71.83 ± 2.1	84.64 ± 6.4
17β-estradiol	0.9985	1.91 ± 0.5	6.37 ± 0.5	84.20 ± 5.9	94.48 ± 4.6

concentration, the highest recovery was achieved for compounds with the highest LogD (dexamethasone and 17β-estradiol) whilst poorer recoveries were obtained for etilefrine and methocarbamol, which had significantly lower LogD values. When factoring the water solubility (Table 1), the results suggested that a fully organic extraction solvent such as 100 % methanol could improve the recoveries obtained. Another factor considered that may have influenced the recovery was suppression from matrix effects [51]. The addition of sample clean-up steps would have likely reduced such matrix effects; however, it would have also introduced undesired selectivity to the suspect screening [52]. The average recovery of the target analytes at the two spiking levels ranged from 70– 89 % for nevirapine and 17β-estradiol respectively. This was deemed analytically acceptable since the generally accepted range of recovery is 70– 120 % [53]. To date, there are no other studies on the quantification of pharmaceuticals in paper-based samples using UHPLC-Q Orbitrap HRMS, hence, the performance of the proposed analytical method could not be evaluated against another reported method. Further studies are required to expand and explore the prevalence and possible propagation of pharmaceuticals in the paper recycling chain.

3.2. Occurrence of pharmaceuticals in paper-based samples

Carbamazepine, dexamethasone, ketoprofen, and 17β-estradiol were detected and quantified in 15 of the 42 samples analysed (Fig. 3). 17β-estradiol was found to occur in the highest concentrations with its maximum level found in a paper shopping bag at 697.49 ng/g collected from a recycling facility followed by a recycling facility newspaper sample (498.28 ng/g) and an infant bathtub box from household waste

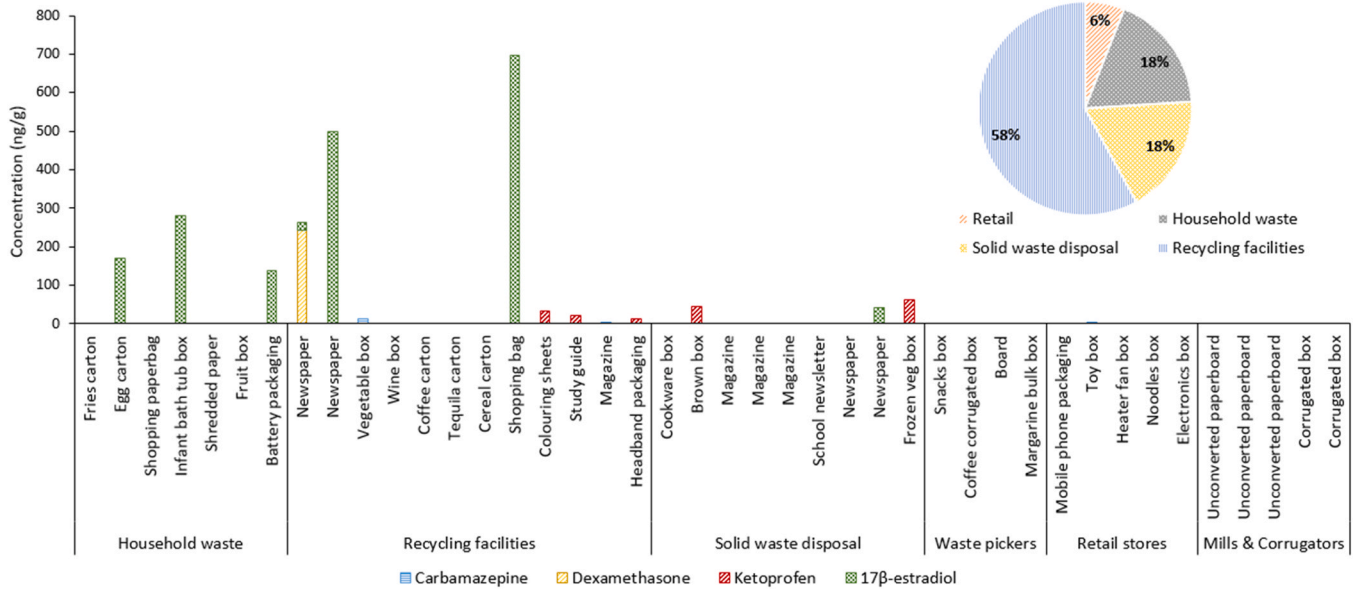


Fig. 3. Pharmaceutical occurrence in paper-based samples.

(280.62 ng/g). From Fig. 3, it was evident that the target pharmaceuticals were detected more in post-consumer samples than in retail or pre-consumer samples. In this case, 58 % of the target pharmaceuticals were detected in samples collected from recycling facilitates, 18 % from solid waste disposal sites, and another 18 % from household waste; in comparison, retail and pre-consumer samples constituted 6 % and 0 %, respectively. Dexamethasone was detected in a newspaper sample (241.48 ng/g) collected at a recycling facility. Carbamazepine was on the other hand, detected in retail store samples (toy box at 4.43 ng/g) and recycling facility samples (a vegetable box at 13.02 ng/g and a magazine at 2.12 ng/g). The detected pharmaceuticals were predominantly found at the household waste, recycling facilities, and solid waste disposal sites which suggested that pharmaceutical exposure likely occurred from exposure to consumers and the mingling of waste, as opposed to the use of pharmaceutical-contaminated water in the paper manufacturing process. The prominence of carbamazepine, dexamethasone, ketoprofen, and 17β-estradiol, over the other target compounds, may have also been due to their chemical properties allowing them to adhere well to paper fibre. The occurrence of 17β-estradiol could be possibly linked to naturally occurring oestrogens, oral contraceptives, and hormone therapy [54]. A study by Olatunji et al. [55] reported that surface water from the city of Cape Town was found to contain estriol and 17β-estradiol with maximum concentrations of 45.5 μg/L and 15.7 μg/L, respectively [55]. This indicated that 17β-estradiol prevalence or use in Cape Town may have contributed to higher concentrations in the samples under investigation. In recent years, 17β-estradiol has also been reported in food matrices [56,57]. Pu et al. [57] identified human and animal excreta, industrial waste, hospital waste, and animal residues as possible sources of 17β-estradiol in animal and plant-derived foods [57]. These same exposure pathways could interact with consumer goods such as paper and could have led to their occurrence in this study. The occurrence of ketoprofen was linked to its possible use as an anti-inflammatory drug in South Africa [58]. Overall, pharmaceuticals were identified in different types of paper recycling grades including newspaper, paperboard, corrugated board, and carton board, with newspaper samples found to contain three different pharmaceuticals

Table 4
Suspect screening of pharmaceutical compounds.

Pharmaceutical	Therapeutic Class	Sample Description	Site	RT (min)	Chemical Formula	Monoisotopic Mass (amu)	Expected Mass (*m/z*)	Observed Mass (*m/z*)	Mass tolerance (ppm)	SI	RSI
Minocycline	Antibiotic	Fries carton	Household waste	8.29	$C_{23}H_{27}N_3O_7$	457.1849	458.1927	458.1964	1.17	737	998
		Heater corrugated box	Retail					458.1964	8.09	743	999
		Cookware box	Solid waste site					458.1963	7.84	725	999
		Coffee corrugated box	Waste picker					458.1967	8.75	747	997
Trioxsalen	Psoralen	Egg carton	Household waste	4.59	$C_{14}H_{12}O_3$	228.0735	229.0813	229.0817	2.28	871	999
		Snacks box	Waste picker					229.0798	6.72	867	999
Bufexamac	NSAID	Margarine bulk box	Waste picker	2.32	$C_{12}H_{17}NO$	223.1207	224.1283	224.1278	3.22	985	985
Flunixin	NSAID	Shopping paperbag	Household waste	7.96	$C_{14}H_{11}F_3N_2O_2$	296.1345	297.1423	297.1418	1.81	737	815
Triflupromazine	Antipsychotic	Shredded paper	Household waste	9.10	$C_{18}H_{19}F_3N_2S$	352.1584	353.1662	353.1656	1.52	758	984
		Coffee corrugated box	Waste picker					353.1657	1.43	788	990
Donepezil	Psychiatric	Newspaper	Solid waste	9.81	$C_{24}H_{29}NO_3$	379.2143	380.2221	380.2199	5.56	765	993
Prazepam	Psychotropic	Shopping paperbag	Recycling facility	4.69	$C_{19}H_{17}ClN_2O$	324.2199	325.2277	325.2272	1.65	925	937
		Coffee corrugated box	Waste picker					325.2272	1.65	927	927
		Noodles box	Retail					325.2272	1.65	951	955
		Colouring sheets	Recycling facility					325.2271	1.96	940	949
Tamoxifen	Hormonal	Study guide	Recycling facility	6.29	$C_{26}H_{29}NO$	371.2255	372.2333	372.2328	1.44	702	985
Chlorphenoxamine	Antihistamine	Tequila carton	Recycling facility	4.07	$C_{18}H_{22}ClNO$	303.1381	304.1459	304.1468	3.05	901	999
Beclomethasone	Corticosteroid	Newspaper	Solid waste	5.65	$C_{22}H_{29}ClO_5$	408.1642	409.1720	409.1715	1.31	772	998
17β-Nandrolone decanoate	Anabolic-androgenic steroid	Shopping paperbag	Recycling facility	11.72	$C_{28}H_{44}O_3$	428.3650	429.3728	429.3722	1.25	775	929
Androsterone sulphate		Study guide	Recycling facility	10.45	$C_{19}H_{30}O_5S$	370.1814	371.1892	371.1896	1.06	716	928
		Newspaper	Solid waste					371.1899	1.95	769	922
Boldenone		Newspaper	Solid waste	6.79	$C_{19}H_{26}O_2$	286.1933	287.2011	287.2002	3.04	795	870
		Unconverted paperboard	Mill					287.2005	1.87	767	867
Theobromine	Vasodilator	Margarine bulk box	Waste picker	2.65	$C_7H_8N_4O_2$	180.0647	181.0725	181.0732	3.65	902	999
		Fries carton	Household waste					181.0732	3.65	898	999

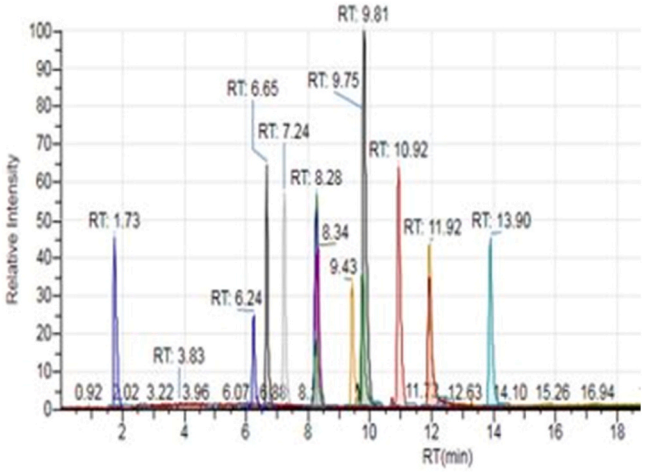


Fig. 4. XIC for newspaper sample.

(241.48 ng/g dexamethasone, 1.47 ng/g ketoprofen and 17β-estradiol at of maximum of 498.28 ng/g). This indicated that exposure to pharmaceuticals occurs in various paper grades with different barrier properties. Further, the identified compounds highlight that complex pathways exist between humans, consumer goods, food, industry, waste management, and the environment and that, practices such as packaging of goods and recycling of material could provide increased opportunities for contact.

3.3. Suspect screening of pharmaceuticals in paper-based samples

Suspect screening was performed in order to identify other possible pharmaceuticals that could be present in the paper-based samples under investigation as shown in Table 4. For this study, all other classes of compounds were not included. The suspect compounds reported were those having mass tolerance (ppm) < 10 ppm, SI> 750, and RSI> 800, to increase the likelihood of correct identification. An illustration of the acquired extracted-ion-chromatograph (XIC) for the newspaper sample collected at a solid waste disposal site is shown in Fig. 4.

The therapeutic class of the suspected pharmaceutical was included in order to apportion to a possible source of contamination. A total of 14 pharmaceuticals (Table 4 and Fig. 5) belonging to different therapeutic classes were tentatively identified in 17 of the 42 investigated samples. The majority of the screened pharmaceuticals were detected from samples collected from recycling facilitates (24 %) and household waste (24 %). The paper grade with the most prevalent suspected occurrence of pharmaceuticals was corrugated board (41 %), followed by cartonboard (18 %). Both corrugated boxes and cartons are used extensively

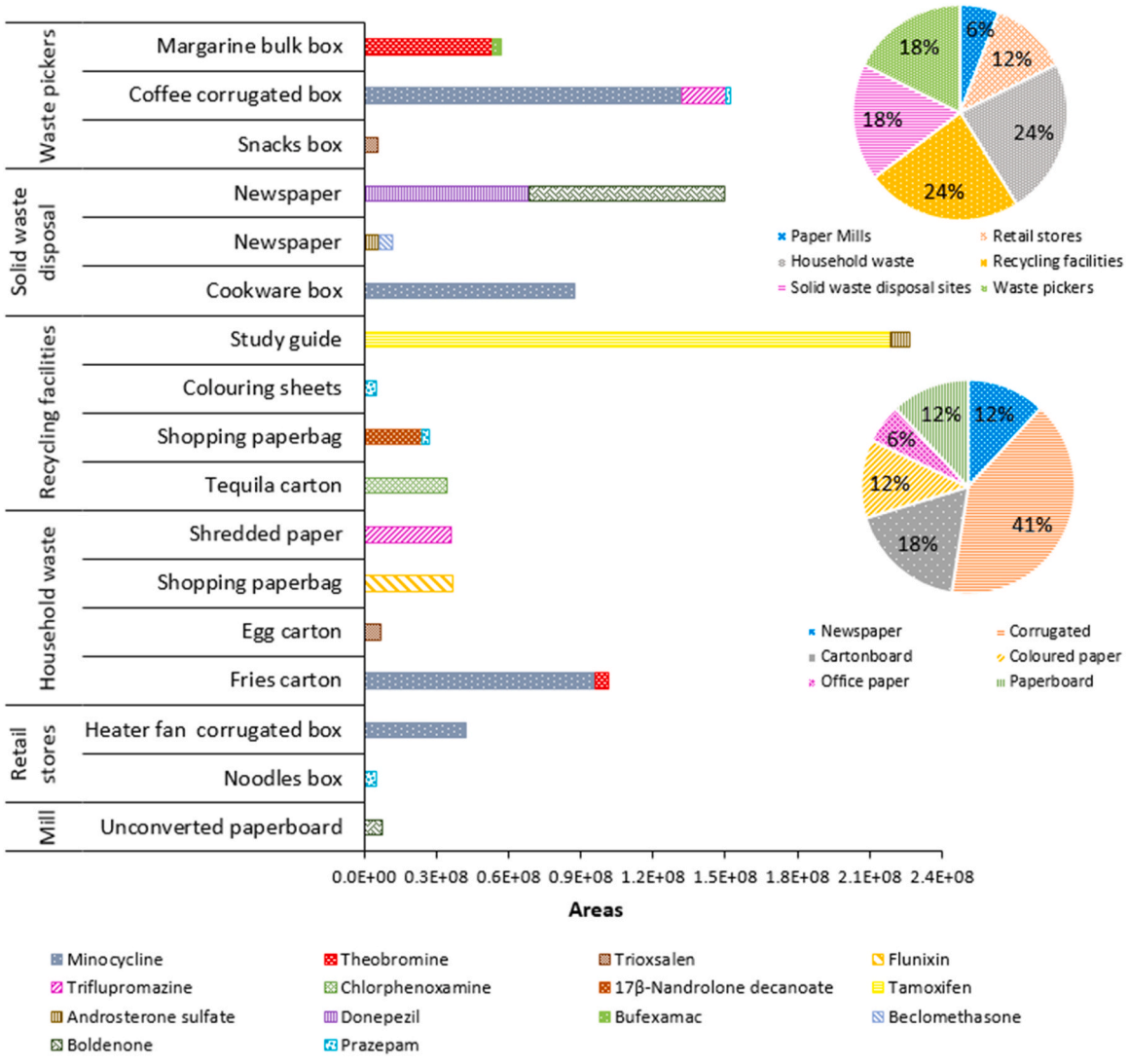


Fig. 5. Possible pharmaceutical prevalence in investigated samples.

for packaging goods and are also integral elements of the paper recycling chain, which would likely have increased exposure opportunities. When looking beyond the therapeutic classes to the application, pharmaceuticals related to skin disorders such as trioxsalen [59], chlorphenoxamine [60], and bufexamac [61] were tentatively identified. This suggested that dermal contact could have resulted in the transfer of these pharmaceuticals to paper materials. The identification of several different anabolic steroids such as 17β-nandrolone decanoate, androsterone sulphate, and boldenone at recycling facilities, solid waste sites, and in a mill sample suggest that certain pharmaceuticals may be more well retained in the fibre lattice of paper throughout the paper recycling chain. Integrated peak areas in the acquired chromatograms were used as measures of the response function of the UHPLC corresponding to the unknown concentrations [62] of the suspected pharmaceuticals. In the absence of chemical standards, the peak areas of the suspected pharmaceuticals were plotted to give an indication of the possible prevalence (Fig. 5). The highest peak area was for tamoxifen (2.19E+08) detected in a study guide collected at a recycling facility. The bufexamac detected in the margarine bulk box from a waste picker had the lowest detected area in the suspect screening with a peak area of 3.12E+ 07. Samples collected from recycling facilities, waste pickers, and household waste were found to have the highest areas in the suspect pharmaceuticals. The higher prevalence of suspect pharmaceuticals in post-consumer samples correlated with the quantified data (Fig. 3) where the highest concentrations were detected in samples collected from recycling facilities and household waste. Although the peak area gave an indication of possible concentration differences for the same compound differentiation, analytical standards would be necessary for accurate comparisons.

4. Conclusion

Overall, this study reported a suitable analytical method that proved to be useful in the analysis of both targeted pharmaceuticals and suspect screening of the same compound classes in paper-based samples. The analytical approach was based on UAE of pharmaceuticals followed by the analysis with UHPLC-HRMS. This work highlighted the importance of understanding the chemical interface between industry, consumers, and the environment. Waste management protocols used for the recovery, collection, sorting, and co-mingling of waste material likely influenced the presence of pharmaceuticals in the paper samples. The highest concentration of pharmaceuticals was identified in post-consumer samples in household waste and at recycling facilities with 17β-estradiol being the most prevalent pharmaceutical. The absence of the target pharmaceuticals in pre-consumer samples suggested that pharmaceutical contamination may not be as substantial in the paper manufacturing and converting stages. Suspect screening enabled tentative identification using the power of HRMS. The suspect screening indicated the need for accurate quantification with the use of reference standards. Although trace-level concentrations of pharmaceuticals were identified, more work is needed to understand the risk posed by pharmaceuticals, the possible effects on human health, the different exposure pathways, and how consumer usage and contact patterns affect the prevalence of these compounds. This study indicated the proliferation of pharmaceutical contamination beyond environmental media. It further emphasised the importance of building more knowledge into emerging contaminants that may be present in paper-based material and the crucial need to influence policy driven towards proper waste management protocols that can improve the quality of recycled material for consumers and the environment.

Environmental implications

This study is the first reported pharmaceutical contamination of paper. Pharmaceuticals are emerging contaminants that have been detected in environmental media such as water, soil, and plants. Their detection in paper recycling is thereby important in showing the proliferation of pharmaceuticals beyond traditional sources and sinks. It identifies the need for further evaluations of exposure pathways in future risk assessments. The study highlights the intertwining linkages between consumer products, healthcare, waste management, environmental pollution, and the manufacturing industry.

CRediT authorship contribution statement

Nondumiso N. Mofokeng: Writing – original draft, Project administration, Methodology, Formal analysis. **Lawrence M. Madikizela:** Writing – review & editing, Supervision, Project administration, Formal analysis, Conceptualization. **Ineke Tiggelman:** Writing – review & editing, Validation, Supervision, Resources. **Luke Chimuka:** Writing – review & editing, Supervision, Project administration, Conceptualization.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Nondumiso Mofokeng reports funding was provided by Mpact Operations Pty (Ltd). All other authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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