Human Health Risk-based Prioritization of Endocrine-disrupting Chemicals in Water-A Perspective

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Abstract

Endocrine-disrupting chemicals ("EDCs", hereafter) have attracted special attention due to its reported toxic effects on children, pregnant woman and elderly. Current EDC-based prioritization approaches do not explicitly include human health risks. This study proposed a theoretical perspective on development of a human health risk-based prioritization framework for monitoring endocrine-disrupting chemicals (EDCs) in water (termed as "EDCriskrank" framework, hereafter), addressing the issue of selecting prioritized EDCs based on human health risk criterion. Applicability of the proposed EDCriskrank framework is illustrated by preparing teratogenicity-based priority list using endocrine-disrupting chemicals in U.S. finished drinking with specific focus for pregnant women. The teratogenicity-based list consisted of endocrine-disrupting chemicals in following order (in increasing priority): Flumequine < 19-norethisterone < mestranol = estriol (out of 5 endocrine-disrupting chemicals considered). The developed list could be used for monitoring chemicals in water and explicitly incorporates teratogenicity-based human health risks as compared to other studies. Future work involves implementation of the proposed framework for Indian waters is required to help Indian wastewater treatment plant operators in protecting human health.

Keywords: Endocrine-disrupting chemicals, drinking water, human health risk assessment, ranking

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1. Introduction

Endocrine-disrupting chemicals ("EDCs", hereafter) have attracted special attention of most of the researchers due to its effect on sensitive subpopulation, such as pregnant woman and elderly [*1, 2*]. Prioritization approaches for selecting important EDCs in surface and finished waters, based on criteria, such as occurrence, treatment in water treatment plants, ecotoxicity effects and human health effects, are available [*3-8*]. For example, Kumar and Xagoraraki [*8*] prioritized 38 EDCs in U.S. finished drinking waters using the EOCRank prioritization methodology presented in the Kumar and Xagoraraki [*7*] study and developed a short list of 20 prioritized EDCs. However, these prioritization approaches, such as EOCRank [*7*] do not include quantitative pharmaceutical risk assessment step [*3, 9-11*]. Table 1 shows summary of some of the previous studies on pharmaceuticals ranking and risk assessment. Review of these studies indicates that not many studies have focused on both ranking and assessing risks due to exposures to pharmaceuticals together. Few studies have focused mainly on ranking of compounds [*4, 6, 7, 12, 14-17*] whereas some studies have focused on assessing risks regardless of ranking of chemicals [*2, 9-11, 18-24*].

To aid water utilities in finalizing EDCs in raw and treated waters at drinking water treatment plants, development of an integrated EOCRank system with a quantitative pharmaceuticals risk assessment framework involving a decision tree-based framework is required. The objective of this communication was to propose a theoretical perspective on development of a human health risk-based prioritization framework for monitoring EDCs in water ("EDCriskrank" framework, hereafter). This framework is expected to provide a quantitative framework for addressing the issue of selecting prioritized EDCs based on human health risk criterion. The approach consists of selecting pharmaceuticals based on human health risks is an important step as it helps in finding out if a particular EDC under consideration poses human health risks for a given environmental exposure scenario and warrants observation in environment and/or removal at water treatment plant level. Application of the proposed framework is shown using endocrine-disrupting chemicals in U.S. finished waters.

2.0. The "EDCriskrank" Framework-A Perspective

The proposed "EDCriskrank" framework is a perspective, combining requirements of both ranking and human health risks aspects of exposures to pharmaceuticals from water, differing from previously used approaches (Table 1). This proposed perspective consists of four steps, which are presented below including related-theoretical considerations, issues/uncertainties and data needs.

2.1. Step 1: Development of a Priority List of EDCs in Finished Waters (List #1)

The first step of the development of the proposed EDCriskrank involves (1) Identification of EDCs-of-concern and (2) Development of a priority list of EDCs in finished waters (termed as List #1, hereafter). This information can be obtained from recently developed emerging organic compounds-based databases. For example, the EOCRank system, developed for prioritizing EOCs in U.S. waters by Kumar and Xagoraraki [*7*] at Michigan State University (U.S.A.) can be used to identify EDCs-of-concern in U.S. finished and surface waters. A short list of prioritized 5

EDCs out of total 38 EDCs in U.S. finished waters, obtained from the Kumar and Xagoraraki [*8*] study, is presented in Table 2. In addition, information about data availability of different health effects due to these chemicals, such as carcinogenicity (i.e., potential of getting a cancer), endocrine effects, teratogenicity (i.e., potential of affecting pregnant women), mutagenicity (i.e., potential of interfering with genes), impairment of fertility, central nervous system acting, immunotoxicity, and developmental effects (i.e., potential of affecting fetus).

2.2. Step 2: Quantitative Pharmaceuticals Risk Assessment of Prioritized EDCs

The second step involves integration of the EOCRank system for EDCs, adapted from the Kumar and Xagoraraki [*7*] study with the quantitative pharmaceuticals risk assessment step, previously used for different pharmaceuticals in environmental waters [*9-12*]. A typical quantitative pharmaceuticals risk assessment involves four steps: (1) Hazard identification, (2) Exposure assessment, (3) Dose-response relationship, and (4) Risk characterization. Each of these steps requires information about pharmaceutical type, their physical and chemical properties and dose-response data for human subjects and currently possesses some data gaps, needing more research work and data collection [*9-12*]. The final step of the quantitative pharmaceuticals risk assessment methodology involves estimation of hazard quotient (HQ) representing ratio of chronic daily intake (CDI) of pharmaceuticals to acceptable daily intake (ADI) for a particular exposure scenario (Equation 1).

$$HQ = \frac{CDI}{ADI} \tag{1}$$

Chronic daily intake of a pharmaceutical compound from water depends on ingestion rate (IR), pharmaceutical concentration in water (CW), and body weight (BW) of the selected subpopulation (Equation 2). Pharmaceutical concentrations can be obtained from monitoring of water or from national monitoring studies. Values of ingestion rate and body weight parameters can be obtained from standard exposure factors databases, as used previously [*9-12*].

$$CDI = \frac{(IR) \times CW}{BW} \tag{2}$$

Acceptable daily intake of a pharmaceutical compound (ADI) indicates that value of the daily intake which does not result in any adverse health effects from direct exposure in a population, including all sensitive subpopulations [*10*] and is calculated using Equation 3.

$$ADI = \frac{POD}{BW \times UF_{composite}} \tag{3a}$$

$$UF_{composite} = \prod_{i=1}^{5} UF_i \tag{3b}$$

Where, POD represents point-of-departure (i.e., the lowest observed dose which may result in an effect in humans or no observable effects; [*19*]) and $UF_{composite}$ represents composite uncertainty

factor, consists of (1) inter-species variability (i.e., among species), (2) intra-species variability (i.e., within humans), (3) extrapolation from a low-observable-adverse-effect-level to no-observable-adverse-effect level, (4) duration of exposure in toxicological studies (i.e., sub-chronic to chronic), and (5) quality of data [*10*]. This information for different EDCs can be obtained from different toxicity-based studies and governmental databases [*2, 5-7, 9, 10, 13, 15-16, 18*; the RxList internet drug index, www.rxlist.com).

Using chronic daily intake and acceptable daily intake values, values of hazard quotients for different EDCs are calculated and compared with 1 to determine if the EDC under consideration poses human health risk. A hazard quotient of value greater than 1 indicates that chronic value intake value is higher than the acceptable daily intake value, suggesting a possibility of risk of exposure and warrants remedial actions. Using Monte Carlo uncertainty analysis, different estimates of hazard quotient values (generally N=10,000 estimated values) can be calculated using 10,000 simulated values of different parameters (from Equations 2 &3) using their developed model distributions as per the methodology given in the Kumar and Xagoraraki [*11*] study. For every parameter (Equations 2 & 3), model distributions are developed to reflect parametric and measurement uncertainties in their respective estimates. Further, using 10,000 estimated hazard quotient values, estimates of average and 99th percentile values of hazard quotient for every EDC can be estimated. The use of 99th percentile value of HQ is preferred over average estimate of HQ as the latter do not completely represent the uncertainty involved in HQ estimates. In addition, the use of 99th percentile value of HQ estimate for comparison purposes provides a test if the maximum possible value of HQ under the worst-case scenario considered exceeds 1 or not. These obtained HQ estimates are further used in the Step 3 for developing risk estimates-based priority list of EDCs in water.

2.3. Step 3. Development of a Pool of HHRA-based Priority EDCs (List #2)

This step involves ranking of prioritized EDCs based on human health risk estimates for taking immediate attention. In this regard, first calculated HQ values of different EDCs (from Step 2) are compared with 1 and EDCs with 99th percentile HQ values greater than 1 are identified. These identified EDCs pose human health risk under the exposure scenario considered and constitute a pool of HHRA-based priority EDCs (termed as List #2, hereafter).

The List #2 EDCs require removal at drinking water treatment plant (DWTP) level before water is supplied for human consumption. Further, the List #2 EDCs can be analyzed further to identify EDCs requiring different levels of attention and attention. For example, the List #2 EDCs can be ranked in decreasing order of their HQ values to identify top 10% of EDCs, requiring immediate attention and pooled together as the List #3 EDCs. Towards taking remedial actions, the List #3 EDCs pose serious human health risks and should be addressed first to ensure human health.

2.4. Step 4: Identification of Required Efficient Treatment Trains for EDC Removal at Drinking Water Treatment Plant

This step involves identification of treatment requirements of different drinking water treatment plants for the identified List #2 and List #3 EDCs. Table 3 shows literature reported overall removals of 35 EDCs in full-scale drinking water treatment, identified from the EOCRank system (*7*). It also shows that removal data for 19 out of 35 EDCs are not available and poses a large data gap and knowledge in terms of their fate in DWTP and concentrations in finished drinking water.

Table 4 presents a categorization of EDCs based on their removals in conventional treatment plant (i.e., a plant using combination of filtration (sand), clarification, granular activated carbon adsorption, and chlorination unit processes) and advanced treatment plant (i.e., a plant using ozonation, ultra-violet irradiation, membrane filtration unit processes in addition to conventional treatment plant unit processes). Removal values of EDCs in two drinking water treatment plants are obtained from literature [*25, 26*]. This table provides initial screening information about removal effectiveness of different unit processes for different EDCs (Group A EDCs: >90% removal and Group B EDCs: less than 90% removal) and can be used to understand the model updating/retrofitting or re-designing requirements of the existing drinking water treatment plants under consideration. This information indicates that knowledge and data gaps about fate of EDCs in drinking water treatment plants still exist. Further research work and treatment studies are required to understand fate of these remaining EDCs to properly characterize the finished drinking water before supplying it for human consumption.

3.0. Case Study: Endocrine-disrupting Chemicals in U.S. Finished Waters

The applicability of the proposed EDCriskrank framework is illustrated using endocrine-disrupting chemicals in U.S. finished drinking waters. The List #1, consists of 5 endocrine-disrupting chemicals out of 38 endocrine-disrupting chemicals, was obtained from the Kumar and Xagoraraki [*8*] study (Table 5). Teratogenicity-related health risks due to these endocrine-disrupting chemicals (Table 5) for pregnant women were considered as pregnant women belong to sensitive subpopulation group and require special attention.

Acceptable daily intake of these endocrine-disrupting chemicals depends on their respective pregnancy categories (Pregnancy category: A-Possibility of fetal harm appears remote, B-Animals show no risk, or animal studies suggest risk but human studies show no risk, C-Animal studies show risk but human studies are inadequate, or no adequate studies are available, D-Human studies show some evidence of risk, and X-Animal or human studies show fetal harm, and risks clearly outweigh benefits) [*27*]. Among five chemicals from the List #1 (Table 5), mestranol and estriol belong to the class X category compared to 19-norethisterone (class D) and flumequine (class C). As pregnancy category increases from A to X, teratogenicity increases, which results in decrease in acceptable daily intake values. Thus, as a result, it increases hazard quotient values for similar environmental concentration and other exposure conditions. Thus, order of chemicals in increasing order of hazard quotient values is:

$$\mathbf{HQ_{flumequine} < HQ_{19\text{-}norethisterone} < HQ_{mestranol} = HQ_{estriol}}$$

Using these HQ values, teratogenicity-based List #2 is developed and presented in Table 5. Further, detailed ranking study is required to prioritize all endocrine-disrupting chemicals in water.

4.0. Conclusions

This study presented a theoretical perspective on development of a human health risk-based prioritization framework (i.e., EDCriskrank) for monitoring EDCs in water. This perspective combines requirements of both ranking and human health risks aspects of exposures to pharmaceuticals from water, differing from previously used approaches (Table 1). Four steps were proposed to develop the framework and different data needs for each of these four steps

were discussed. Further, applicability of the proposed EDCriskrank framework is illustrated by preparing List #1 and List #2 using endocrine-disrupting chemicals in U.S. finished drinking waters and conducting teratogenicity-based health risk assessment for pregnant women. The teratogenicity-based List #2 consists of endocrine-disrupting chemicals in following order (in increasing priority): Flumequine < 19-norethisterone < mestranol = estriol. The developed list could be used for monitoring chemicals in water and explicitly incorporates Teratogenicity-based human health risks as compared to other studies. Future work involves implementation of the proposed framework for Indian waters using literature-reported occurrence data on EDCs, pharmaceuticals, and antibiotics in Indian wastewater effluents and streams [*28-30*].

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349 ***Table 1. Considerations of Ranking and Risk Assessment in Previous Pharmaceuticals-based Studies***

Reference	**Contaminant of concern**	**Ranking approach/model**	**Risk Assessment Findings**
Calabrese et al. [12]	15 Endocrine-disrupting chemicals	Toxicologically-based predictive scheme	Not applicable
Sanderson et al.[4]	2986 pharmaceuticals (51 classes)	Quantitative-structure and activity relationship modeling	Not applicable
Baun et al. [14]	233 Xenobiotic organic compounds	Tiered screening approach	Not applicable
Cooper et al. [6]	200 prescription drugs	Multi-attribute utility theory	Not applicable
Schriks et al. [15]	50 chemicals	Threshold of toxicological concern (TTC) approach	Not applicable
Kumar and Xagoraraki [7]	100 chemicals (including pharmaceuticals, personal care products and endocrine-disrupting chemicals)	Multi-attribute utility-theory	Not applicable
Christensen [16]	17α-ethinylestradiol (EE2), phenoxymethylpenicillin (Pen V), Cyclophosphamide (CP)	No ranking	Negligible human risks
Schulman *et al.* [17]	Acetylsalicylic acid, clofibrate, cyclophosphamide, indomethacin	No health risks	No health risks
Webb *et al.* [9]	Acetyl salicylic acid, clofibric acid, ibuprofen, gemfibrozil, fenoprofen, ketoprofen, diclofenac, fenofibric acid, bezafibrate, indometacine, salicylic acid, atenolol, sotalol, salbutamol, terbutalin, fenoterol, nadolol, metropolol, celiprolol, carazolol, clenbuterol, phenazone, ifosfamide, cyclophosphamide, carbamazepine, pentoxifylline, clofibrate, phenazone, dimethlaminophenazon, ifosfamide, cyclophosphamide, carbamazepine, pentoxifylline, diazepam, fenofibrate, etofibrate, clarithromycin, dehydrato-erythromycin, roxithromycin, sulfamethazine, sulfamethoxazole, trimethoprim, chloramphenicol, chloroteracycline, doxycycline, tetracycline, cloxacillin, dicloxacillin, methicillin, nafcillin, oxacillin, benzylpenicillin, phenoxymethylpenicillin, iopamidol, iopromide, ioxithalamic acid, iothalamic acid, diatrizoate, 17α-Ethinylestradiol	Low possibility of health risks	Low possibility of health risks
Schwab *et al.* [10]	Acetaminophen, ablution, cimetidine, ciprofloxacin, codeine,	No ranking	No appreciable

	dehydronifedipine, digoxigenin, digoxin, diltiazem, doxycycline, enalaprilat, erithromycin-H2O, fluoxetine, gemfibrozil, ibuprofen, lincomycin, metformin, norfloxacin, oxytetracycline, paroxetine metabolite, ranitidine, sulfamethoxazole, sulfathiazole, tetracycline, trimethoprim, warfarin		risks to humans
Watts *et al.* [18]	396 pharmaceuticals and 11 illicit drugs	No ranking	No human health risks
Bercu *et al.* [19]	Atomoxetine,duloxetine, olanzapine (neuropharmaceutical compounds)	No ranking	No appreciable health risks
Snyder [2]	Atenolol, atorvastatin, carbamazepine, diazepam, diclofenac, enalapril, fluoxetin, gemfibrozil, meprobamate, naproxen, phenytoin, risperidone, simvastatin, sulfamethoxazole, triclosan, trimethoprim	No ranking	No health risks
Johnson *et al.* [20]	Cytotoxic chemotherapy drugs (5-fluorouracil, cyclophosphamide, epirubicin/doxorubicin)	No ranking	No health risks
Rowney *et al.* [21]	Three cytotoxic drug groups: alkylating agents (oxaliplatin, temozolomide, cisplatin, carboplatin, cyclophosphamide), antimetabolites (gemcitabine, fludarabine, fluorouracil-a metabolite to the prodrug capecitabine), and anthracycline antibiotics (epirubicin, doxorubicin).	No ranking	No health risks
Cunningham *et al.* [22]	44 active pharmaceutical ingredients marketed by GlaxoSmithKline	No ranking	No ranking; No appreciable health risks
Cunningham *et al.* [23]	Carbamazepine and its metabolites (carbamazepine diol and carbamazepine N-glucuronide)	No ranking	No appreciable health risks
Crider *et al.* [24]	Penicillins, erythromycins, cephalosporins, sulfonamides, quinolones, tetracyclines, aminoglycosides, and nitrofurantoins	No ranking	No health risks
Kumar and Xagoraraki [11]	Carbamazepine, phenytoin, meprobamate in U.S. surface water and finished drinking water	No ranking	No appreciable health concern
This study	**100 EDCs obtained from the EOCRank database**	**Ranking-based risk assessment proposed**	

EDCs-Endocrine-disrupting chemicals, PPCPs-Pharmaceuticals and personal care products, NA-Not applicable

Table 2. Prioritized Five Endocrine-disrupting Chemicals in U.S. Finished Drinking Waters

Name (Priority*)	**Use/Effect****	**Health-related Data Availability#**	**Health-related Data Gaps#**
Mestranol [$] (Priority 1)	Pharmaceuticals/Teratogenic compounds (reproductive hormone)	Teratogenicity (Class X), Carcinogenicity, Endocrine effects	Mutagenicity; Impairment of fertility; CNS acting; Immunotoxicity; Development effects
19-norethisterone[$] (Priority 2)	Pharmaceuticals/Teratogenic compounds (ovulation inhibitor)	Teratogenicity (Class D), Impairment of fertility, Developmental effects	Carcinogenicity; Mutagenicity; CNS acting; Immunotoxicity
Flumequine[$] (Priority 3)	Pharmaceuticals/Teratogenic compounds/ Antibiotics	Teratogenicity (Class C), Central nervous system acting, Endocrine effects	Carcinogenicity; Mutagenicity; Impairment of fertility; Immunotoxicity; Development effects
Estriol [$] (Priority 4)	Pharmaceuticals/Teratogenic compounds	Teratogenicity (Class X), Carcinogenicity, Endocrine effects	Mutagenicity; Impairment of fertility; CNS acting; Immunotoxicity; Development effects
Bis(2-ethylhexyl)phthalate (Priority 5)	Pesticide	Carcinogenicity, Endocrine effects	Teratogenicity; Mutagenicity; Impairment of fertility; CNS acting; Immunotoxicity; Development effects

CNS-Central nervous system acting

* Adapted from the Kumar and Xagoraraki [8] study.

**Teratogenic compounds-Those compounds which can affect pregnant woman

#Pregnancy category: A-Possibility of fetal harm appears remote, B-Animals show no risk, or animal studies suggest risk but human studies show no risk, C-Animal studies show risk but human studies are inadequate, or no adequate studies are available, D-Human studies show some evidence of risk, and X-Animal or human studies show fetal harm, and risks clearly outweigh benefits.

Notations: Pharmaceuticals: Chemicals with suffix [$]; Personal care products: chemicals with suffix [#]; Antibiotics: italicized chemicals; Teratogenic compounds: underlined chemicals

362 ***Table 3. Overall Removals of EDCs during Full-Scale Drinking Water Treatment***

ID	Name	Location	Influent Conc. (ng/L)	Overall Removal (%)*	Scheme ID: Treatment schemes*	Reference
1	Fluoxetine[$]	U.S.A.	0.8	100	Preoxidation (Cl_2), coagulation/flocculation, sedimentation, chlorination, filtration, and chloramination	[25]
2	*Triclosan[$]*	U.S.A.	1.5	20	Coagulation/flocculation, sedimentation, ozonation, dual-media filtration, and chloramination	[25]
3	Atrazine	U.S.A.	85	11.8	Preoxidation (Cl_2), coagulation/flocculation, sedimentation, chlorination, filtration, and chlorination	[25]
		U.S.A.	1.8	51	Preoxidation (Cl_2), ozonation, coagulation/flocculation, filtration, and chlorination	[25]
		U.S.A.	770	64	Preoxidation (ClO_2), coagulation/flocculation, sedimentation, filtration, ultraviolet irradiation, and chlorination	[25]
		U.S.A.	780	69	Preoxidation and intermediate oxidation (O_3), coagulation/flocculation, sedimentation, GAC/sand bio-filtration, and chloramination	[25]
		U.S.A.	94	64	Preoxidation (Cl_2), coagulation/flocculation, sedimentation, chlorination, filtration, and chloramination	[25]
		U.S.A.	5.7	82.6	Coagulation/flocculation, sedimentation, ozonation, dual-media filtration, and chloramination	[25]
4	4-nonylphenol	U.S.A.	88	9	Coagulation/flocculation, sedimentation, chlorination, and chloramination	[25]
		U.S.A.	130	23	Preoxidation (ClO_2), coagulation/flocculation, sedimentation, filtration, ultraviolet irradiation, and chlorination	[25]
		U.S.A.	99	23	Preoxidation (Cl_2), coagulation/flocculation, sedimentation, chlorination, filtration, and chloramination	[25]
		U.S.A.	342	73	Screening, clarification, chlorination, sand/GAC filtration, secondary chlorination	[26]
5	Bisphenol A	U.S.A.	14	64	Coagulation/flocculation, sedimentation, chlorination, and chloramination	[25]
		U.S.A.	107	76	Screening, clarification, chlorination, sand/GAC filtration, secondary chlorination	[26]
6	Diazinon	U.S.A.	47	100	Screening, clarification, chlorination, sand/GAC filtration, secondary chlorination	[26]
7	Methyl parathion	NA				[26]

8	Carbaryl	U.S.A.	55	100	Screening, clarification, chlorination, sand/GAC filtration, secondary chlorination	[26]
9	Chlorpyrifos	NA				
10	Diethylphthalate	NA				
11	Bis(2-ethylhexyl)phthalate	NA				
12	2,6-di-tert-butyl-1,4-benzoquinone	NA				
13	Benzo(a)pyrene	NA				
14	Pentachlorophenol	NA				
15	Lindane	NA				
16	Cis-chlordane	NA				
17	Dieldrin	NA				
18	2,6-di-tert-butylphenol	NA				
19	3-tert-butyl-4-hydroxy anisole	NA				
20	Estriol[$]	NA				
21	17 α –ethynyl estradiol[$]	NA				
22	Cis-androsterone[$]	NA				
23	19-norethisterone[$]	NA				
24	17β-Estradiol[$]	NA				
25	Mestranol[$]	NA				
26	Estrone[$]	U.S.A.	0.9	39	Preoxidation (Cl_2), coagulation/flocculation, sedimentation, chlorination, filtration, and chloramination	[25]
		U.S.A.	0.33	39	Preoxidation (ClO_2), coagulation/flocculation, sedimentation, filtration, ultraviolet irradiation, and chlorination	[25]
		U.S.A.	0.3	100	Preoxidation (Cl_2), coagulation/flocculation, sedimentation, chlorination, filtration, and chlorination	[25]
		U.S.A.	0.2	100	Preoxidation (Cl_2), coagulation/flocculation, sedimentation, filtration, and chloramination	[25]
		U.S.A.	0.4	100	Coagulation/flocculation, sedimentation, ozonation, dual-media filtration, and chloramination	[25]

		U.S.A.	0.63	100	Preoxidation and intermediate oxidation (O_3), coagulation/flocculation, sedimentation, GAC/sand bio-filtration, and chloramination	[25]
27	17α-estradiol[$]	NA				
28	Progesterone[$]	U.S.A.	1.8	72.2	Coagulation/flocculation, sedimentation, chlorination, and chloramination	[25]
		U.S.A.	3.1	100	Preoxidation (Cl_2), coagulation/flocculation, sedimentation, filtration, and chloramination	[25]
		U.S.A.		100	Preoxidation (Cl_2) and chloramination	[25]
		U.S.A.	0.54	100	Preoxidation (Cl_2), ozonation, and chloramination	[25]
29	Equilenin[$]	NA				
30	Testosterone[$]	U.S.A.	0.9	44	Coagulation/flocculation, sedimentation, chlorination, and chloramination	[25]
31	Equilin[$]	NA				
32	HHCB[#]	U.S.A.	32	22	Coagulation/flocculation, sedimentation, chlorination, and chloramination	[25]
		U.S.A.	69	100	Screening, clarification, chlorination, sand/GAC filtration, secondary chlorination	[26]
33	AHTN	U.S.A.	126	71.4	Screening, clarification, chlorination, sand/GAC filtration, secondary chlorination	[26]
34	Linuron	U.S.A.	4.1	100	Coagulation/flocculation, sedimentation, ozonation, dual-media filtration, and chloramination	[25]
35	Metolachlor	U.S.A.	17	11.8	Preoxidation (Cl_2), coagulation/flocculation, sedimentation, chlorination, filtration, and chlorination	[25]
		U.S.A.	46	100	Screening, clarification, chlorination, sand/GAC filtration, secondary chlorination	[26]
		U.S.A.	28	100	coagulation/flocculation, sedimentation, ozonation, dual-media filtration, and chloramination	[25]

AHTN- 7-acetyl-1,13,4,4,6-hexamethyl-1,2,3,4-tetrahydronaphthalene; HHCB- 1,3,4,6,7,8- hexahydro-4,6,6,7,8,8-hexamethylcyclopenta-(γ)-2-benzopyran; NA: not available

*Treatment schemes with >90% EDCs removals are highlighted as shaded texts

** Notations: Pharmaceuticals: Chemicals with suffix [$]; Personal care products: chemicals with suffix [#]; Antibiotics: italicized chemicals; Teratogenic compounds: underlined chemicals

***Table 4. Categorizaton of EDCs based on their removals in drinking water treatment plants: (a) Conventional treatment: Combination of filtration (sand), clarification, GAC adsorption, and chlorination unit processes and (b) Advanced treatment: Combination of conventional treatment unit processes with ozonation, ultra-violet irradiation, membrane filtration unit processes) (Removal values for EDCs are obtained from the Benotti et al. (25) and Stackelberg et al (26) studies)*,**

Treatment type	Less than 90% removal (Category B-EDCs)	More than 90% removal (Category A-EDCs)
Conventional treatment plant	4-nonylphenol; Bisphenol A; Testosterone[$]; AHTN	Fluoxetine[$]; Carbaryl; Estrone[$]; HHCB[#]; Metolachlor
Advanced treatment plant	*Triclosan[$];*Atrazine; Diazinon	Progesterone[$]; Linuron

Treatment information not available: Methyl parathion; chlorpyrifos; disethylphthalate; dis(2-ethylhexyl) phthalate; 2,6-di-tert-butyl-1,4-benzoquinone, benzo(a)pyrene; pentachloropenol; Lindane; cis-chlordane; dieldrin; 2,6-di-tert-butylphenol; 3-tert-butyl-4-hydroxy anisole; estriol [$]; 17 α –ethynyl estradiol[$]; Cis-androsterone[$] ; 19-norethisterone[$];17β-Estradiol[$]; Mestranol[$];17α-estradiol[$];Equilenin[$];Equilin[$]

*Treatment classification adapted from the Kumar and Xagoraraki [7] study.

** Pharmaceuticals: Chemicals with suffix [1]; Personal care products: Chemicals with suffix [2]; Antibiotics: Italicized chemicals; Teratogenic compounds (i.e., those compounds which belong to be in the pregnancy category): Underlined chemicals

379 ***Table 5. Application of the Proposed EDCriskrank Framework to Endocrine-disrupting Chemicals in U.S. Finished Waters***

Name[*]	**List #1 (Priority without Human Health Risks [8])**	**List #2 (Teratogenicity-based Priority /(Teratogenic Class**[#]**))**
Mestranol [$]	1	1 (Class X)
19-norethisterone[$]	2	2 (Class D)
Flumequine[$]	3	3 (Class C)
Estriol [$]	4	1 (Class X)
Bis(2-ethylhexyl)phthalate	5	Not conducted as data not available

380 [*] Notations: Pharmaceuticals: Chemicals with suffix [$]; Personal care products: chemicals with suffix [#]; Antibiotics: italicized chemicals; Teratogenic
381 compounds: underlined chemicals
382 [#]Pregnancy category: A-Possibility of fetal harm appears remote, B-Animals show no risk, or animal studies suggest risk but human studies show no risk, C-
383 Animal studies show risk but human studies are inadequate, or no adequate studies are available, D-Human studies show some evidence of risk, and X-Animal or
384 human studies show fetal harm, and risks clearly outweigh benefits.
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