Appendix K

Pharmaceuticals and Personal Care Products (PPCPs)

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K.0 Endocrine Disrupting Chemicals (EDCs) and Pharmaceuticals and Personal Care Products (PPCPs)

During the past 30 years, studies of environmental pollutants have concentrated predominantly on conventional pollutants such as dichlorodiphenyltrichloroethane (DDT), polychlorinated biphenyls (PCBs), and chlorinated dioxins that are used in agricultural and industrial activities. However, these conventional pollutants represent a small percentage of the chemicals being released to the environment. The use and disposal of consumer chemicals have become a global issue in recent years. In the last 10 to 12 years, a more concerted effort has been made to research the multitude of other pollutants, including contaminants of emerging concern such as pharmaceuticals and personal care products (PPCPs) and endocrine disrupting chemicals (EDCs), in the environment.

The presence of EDCs and PPCPs in waters is not a new phenomenon. It is reasonable to assume that PPCPs have been discharged to groundwater and surface waters for as long as people have been using them. Likewise, endocrine disrupting steroid hormones were reported to occur in surface water as early as 1965 (Stumm-Zollinger and Fair 1965). However, recent advances in analytical chemistry methods and instrumentation have allowed the detection of progressively smaller concentrations of some EDCs and PPCPs in the environment, and particularly in surface water and in effluents from municipal and industrial wastewater treatment plants (WWTP). It is now apparent that these contaminants are present ubiquitously in the effluents of municipal and industrial WWTP and in surface waters impacted by these effluents, including source waters for drinking water treatment plants. Some of these chemicals also have been reported to appear in raw and finished drinking water in the United States (Lee et al. 2004, Stackelberg et al. 2004) and elsewhere.

Pharmaceuticals found in the environment include both prescription and non-prescription (over-the-counter [OTC]) pharmaceuticals used in human and veterinary medicine. Because some pharmaceutical metabolites and degradates can retain significant bioactivity, the term “pharmaceutically-active chemicals” (PhAC) is sometimes used to encompass these along with the parent compounds. Pharmaceuticals found in the environment include, but are not limited to, analgesics, anti-inflammatories, antibiotics (veterinary and human), antiepileptics, antineoplastics, beta blockers, anti-hyperlipidaemics, diagnostic X-ray contrast media, tranquillizers, narcotics (prescription and illicit), broncholytics, expectorants, and antiparasitics (Puijker and Mons 2004). Some potential sources of pharmaceuticals to the environment include municipal WWTP effluents, hospital effluents, runoff from concentrated animal feeding operations (CAFOs), effluents from pharmaceutical manufacturing facilities, landfill leachate, and urban runoff containing waste from medicated pets. However, municipal WWTP effluents have been identified as a major source of pharmaceuticals (as well as personal care products and EDCs) to surface waters (Lee et al. 2004, Daughton 2001b). Pharmaceuticals enter WWTP when people taking medications excrete pharmaceuticals and their metabolites, rinse them from their bodies during bathing, or flush unused medications down the sink or toilet.

Personal care products are chemicals marketed for direct use by the consumer (excluding non-prescription medication with documented physiological effects) and generally intended to be

applied to the human body rather than ingested (with the exception of food supplements). Most are ingredients or preservatives in cosmetics, toiletries, or fragrances. They are not intended as treatments for disease but may be intended to prevent diseases (e.g., sunscreen agents like oxybenzone, antimicrobial agents like triclosan in hand soap). Caffeine and its metabolite 1,7-dimethylxanthine; the nicotine metabolite cotinine; and the flame retardant chemical tris (2-chloroethyl) phosphate (TCEP) often are classified as personal care products, or as degradates or metabolites of personal care products. Many personal care products are used in very large amounts, and, compared with pharmaceuticals, relatively little is known about their environmental fate or effects. Like pharmaceuticals, personal care products often enter the environment via municipal WWTP effluents. Personal care products such as sunscreen agents and fragrance musks might be released directly to the environment (e.g., washed from the body into surface waters during recreational activities), thus by-passing treatment in WWTP (Daughton and Ternes 1999).

Chemicals with the potential to interfere with endocrine systems are called EDCs. Other terms used to describe these chemicals are "endocrine disruptors," "hormonally active agents" (HAAs), "endocrine active chemicals" (EACs), or similar variations of these. The U.S. Environmental Protection Agency (EPA) (1997) defines endocrine disrupting chemicals as exogenous agents that interfere with the production, release, transport, metabolism, binding, action, or elimination of the natural hormones in the body responsible for the maintenance of homeostasis and the regulation of developmental processes. However, other agencies and organizations use different definitions. The EPA developed the Endocrine Disrupter Screening Program (EDSP) to identify screening methods and toxicity testing strategies that can be used to definitively determine whether a chemical is, or is not, an EDC. This process is incomplete, and there currently is no scientific consensus regarding the criteria that can be used to identify EDCs. Many chemicals have not been tested by any method for potential endocrine activity, and controversy surrounds the assignment of the label "EDC" to many chemicals. However, certain chemicals are widely considered to be EDCs. In this report, the term "EDC" refers to known or potential EDCs.

Endocrine disrupting chemicals include a vast number of chemicals with widely varying structures. For example, the Institute for Environment and Health (IEH 2005) in the United Kingdom identified 966 chemicals or elements that have been suggested in the published literature to be potential endocrine disrupters. Endocrine disrupting chemicals include chemicals arising from natural sources as well as anthropogenic chemicals. Naturally occurring EDCs that enter the aquatic environment include: hormones excreted by humans and discharged in WWTP effluent, hormones excreted by livestock at CAFOs and then washed into runoff from these facilities or leached from manure applied to land, hormones excreted by fish in aquaculture, phytoestrogens and mycoestrogens (produced by plants and fungi, respectively), dioxins produced by forest fires and volcanic activity, and naturally occurring ions like nitrate. Anthropogenic sources of EDCs include: industrial chemicals and their degradation products (PCBs, nonylphenol, bisphenol-A); petroleum products, incinerators, power plants, and vehicle exhaust (PAHs, dioxins); biocides (tributyltin, DDT, chlordane, atrazine), and certain pharmaceuticals (ethinylestradiol, or EE2, an active ingredient in oral contraceptive medications). A small subset of PPCPs, primarily synthetic steroids and other synthetic hormones, are known or suspected to be direct-acting EDCs (Daughton 2001a). Given the wide range of chemicals that can be considered to be EDCs, their sources to the environment and routes of exposure to humans and ecological receptors are numerous, and it is not surprising that many EDCs enter WWTP.

Although wastewater treatment processes are capable of removing EDCs and PPCPs to varying degrees, chemicals that resist degradation many remain in treated effluents discharged to surface waters. In the environment, these chemicals may be subject to dilution and environmental degradation, but some persist in the environment. Even when chemicals are efficiently removed, trace concentrations often can still be detected in effluents due to ultra-sensitive analytical methods. Chemicals that are not persistent in the environment sometimes can still be detected in surface water downstream of WWTP outfalls due to constant loading.

K.1 Regulations

Currently, there are no monitoring, remediation, or regulatory requirements for PPCPs in water in the U.S. (and most other countries). The EPA Office of Research and Development has begun gathering results from studies on the various aspects of PPCPs including:

- Sources and origins,
- Environmental occurrence and distribution,
- Transport and fate,
- Exposure of biological receptors,
- Effects,
- Remediation (engineered treatment processes),
- Pollution prevention, and
- Risk communication and perception.

As of 2004, most research had been devoted to sources and origins, environmental occurrence and distribution, and remediation. Only in the last few years have efforts begun to be invested toward identification of effects, pollution prevention, and risk communication and perception (Daughton 2001a).

As with PPCPs, the concentrations of EDCs in drinking water currently are not regulated in the United States. Although certain contaminants that are regulated in drinking water may be considered to be EDCs, they currently are not regulated on the basis of potential endocrine disruptive effects. To the best of the authors' knowledge, no regulatory limits have been established in the United States for EDCs in municipal WWTP effluents. However, the U.S. Food and Drug Administration (FDA) requires environmental risk assessments for new pharmaceuticals with predicted environmental concentrations greater than 1 μg/L in water.

K.2 Potential Human Exposure and Effects Related to EDCs/PPCPs in Water

The focus of this report is the potential risk to humans and ecological receptors (primarily fish) as a result of exposure to EDCs and PPCPs in surface water of the Las Vegas Wash and Boulder Basin of Lake Mead, as well as potential risks related to exposure of humans to these same chemicals through drinking water drawn from the Boulder Basin as a source.

Risk is the probability of adverse effects resulting from exposure to an environmental agent or mixture of agents (EPA 2005a). Risk results from the interaction of exposure and potential for

effects. Humans are expected to be exposed to waterborne EDCs and PPCPs primarily through drinking water. Other routes of exposure are possible. Inhalational and dermal exposure during showering and bathing with potable water might occur. During recreational activities at Lake Mead, inhalational and dermal exposure and exposure by incidental ingestion of small amounts of water also are possible, but contact with lake water and particularly with the more contaminated water of the Las Vegas Wash generally will be limited. As a result, waterborne exposure to humans occurring through routes other than ingestion of drinking water is expected to be minor for most of the EDCs and PPCPs of interest here.

For many of these contaminants, exposures to people through water are expected to be small compared with potential exposure to the same contaminant received through food and beverages, prescription and non-prescription medications, occupational exposures, and residential activities (e.g., cleaning products, personal care products, hobby chemicals, pesticides). Thus, the relative importance of non-water-related exposures should be considered. Furthermore, people and organisms in the environment are not exposed to individual contaminants but rather to mixture of contaminants, and constituents of these mixtures may interact with or overwhelm the potential effects of EDCs/PPCPs in drinking water.

Table K-1 presents the maximum concentrations of selected EDCs and PPCPs reported to date in surface water samples from the Las Vegas Wash and its tributaries and Las Vegas Bay of Lake Mead. Table K-2 presents concentrations of some EDCs or PPCPs detected in tertiary-treated effluent collected from one of the municipal WWTPs that discharge to the Las Vegas Wash. These tables do not include all of the potential EDCs that have been detected in Boulder Basin of Lake Mead. For example, certain PCBs and their metabolites have been reported to be EDCs and have been detected in fish and sediment samples from the Las Vegas Wash and Las Vegas Bay. Polychlorinated biphenyls are often associated with municipal wastewater and particularly with sewage sludge or sediments downstream of WWTP. Perchlorate is a known EDC arising from the Las Vegas Wash and has been a concern for Lake Mead and for downstream users of the Colorado River. However, perchlorate in the Boulder Basin of Lake Mead does not originate from municipal wastewater but rather from contaminated groundwater arising from past industrial activities and resultant groundwater contamination.

While a wide range of PPCPs and EDCs have been detected in the Boulder Basin of Lake Mead and in WWTP effluents that discharge to the Las Vegas Wash, monitoring efforts for these chemicals in Lake Mead are still in their infancy, and few of the available data have been published in formal reports or in the peer-reviewed literature. The number of target analytes examined to date represents a relatively small subset of the vast number of contaminants of emerging concern that could be considered. For the limited set of contaminants that has been analyzed to date, the number of samples is insufficient to characterize their spatial and temporal variation or their range of concentrations occurring in the Las Vegas Wash and Boulder Basin. For most of the EDCs, and particularly for the PPCPs, the data are insufficient to adequately characterize exposure to aquatic organisms or humans for risk assessment. At best, preliminary, screening-level risk assessments could be undertaken for some of these chemicals because the duration, intensity, and timing of exposure cannot be established.

K.2.1 Pharmaceuticals

Currently, no regulatory guidance exists regarding methods for assessing risks to human health associated with exposure to low concentrations of pharmaceuticals in drinking water. Likewise, no regulatory guidance levels that take into account potential human health risks have been published. Evaluations of the human risk of pharmaceuticals in drinking water have been made by Christensen (1998), Webb (2001), Webb et al. (2003), Schulman et al. (2002), and Schwab et al. (2005). All concluded that no appreciable risk for humans exists at the low levels measured in drinking water. Recently Versteegh et al. (2003) calculated provisional "no-effect levels" for a number of pharmaceuticals detected in Dutch drinking water, based on acceptable daily intake (ADI) or maximum residue levels (MRL) for veterinary pharmaceuticals in milk, and these investigators drew similar conclusions.

Other authors (Schwab et al. 2005, Webb et al. 2003, Webb 2001) have proposed estimating the potential for adverse health effects from exposure to pharmaceuticals in drinking water by comparing exposures one would get from drinking the untreated water to the therapeutic dose, divided by several uncertainty or safety factors to account for uncertainties in extrapolating from these doses to levels that would be safe for different population groups. However, while the dose-response relationships of pharmaceuticals in their target organisms are very well-documented, uncertainty exists about the potential effects of these pharmaceuticals on non-target population groups, or about the effect of such factors as differences in dosing and timing of exposure or exposure to multiple chemicals at the same time (Jones et al. 2004).

Table K-3 lists the pharmaceuticals that have been detected in surface water in the Las Vegas Wash and Lake Mead, their maximum detected concentrations, and their lowest therapeutic doses (i.e., the lowest recommended dosage level indicated on the package labeling, assumed to be the lowest exposure level at which the compound produces the desired pharmacologic effect). The table also shows water concentrations for each pharmaceutical that correspond to the lowest therapeutic dose— these concentrations were calculated assuming a person drinks two liters of water at this concentration every day. Because people do not consume untreated surface water from Lake Mead, this is a conservative exposure assumption for waterborne pharmaceuticals. To provide an additional margin of safety, these therapeutic dose concentrations were divided by a factor of 1,000. As shown, the maximum detected concentrations in water are well below equivalent concentrations calculated based on the lowest therapeutic dose divided by a factor of 1,000. No-effect levels calculated by Versteegh et al. (2003) are also shown, where available. Overall, the maximum detected concentrations in drinking water are a factor of 5 to 120,000 lower than the levels calculated as "safe" using either method, and are far below therapeutic dose levels.

Daughton and Ternes (1999) discussed possible effects of long-term exposure to pharmaceuticals. These could include endocrine disrupting activity, induction of antibiotic resistance, genotoxicity, carcinogenicity, or allergic reactions, as well as effects on reproduction or fetal/ child development. Ongoing studies are working to develop toxicity guidance levels for pharmaceuticals in drinking water that take into consideration the full database of toxicity information for each compound, including information about potential effects to the most sensitive subgroups, such as reproductive and developmental effects, as well as cancer risks. Initial results, however, indicate that water concentrations based on the therapeutic dose divided by a factor of 1,000 will likely be protective of these endpoints.

Table K-1 Maximum Concentrations of Detected PPCPs and EDCs in Surface Water Samples Collected From Las Vegas Wash and Its Tributaries and Las Vegas Bay of Lake Mead.*

Chemical	Maximum Conc. (ng/L)	Sample Location	Chemical Description
1,7-Dimethylxanthine	42	Lake Mead near Saddle Island	Personal care product metabolite, metabolite of caffeine (stimulant)
Acenaphthene	13	Las Vegas Wash at Pabco Road	EDC, polycyclic aromatic hydrocarbon (PAH)
Acetaminophen	51	Las Vegas Wash at Pabco Road	Pharmaceutical, analgesic
Acetophenone	Qualitative	Las Vegas Bay	Personal care product, solvent and production intermediate. [b]
Androstenedione	2.6	Las Vegas Wash at Pabco Road	EDC, hormone
Arsenic	117,300	Kerr-McGee Seeps	EDC, metalloid
Atrazine	1.6	Las Vegas Wash at Pabco Road	EDC, pesticide
Benz[a]anthracene	19	Las Vegas Wash at Pabco Road	EDC, polycyclic aromatic hydrocarbon (PAH)
Benzo[a]pyrene	15	Las Vegas Wash at Pabco Road	EDC, polycyclic aromatic hydrocarbon (PAH)
Benzo[b]fluoranthene	16	Las Vegas Wash at Pabco Road	EDC, polycyclic aromatic hydrocarbon (PAH)
Benzo[k]fluoranthene	22	Las Vegas Wash at Pabco Road	EDC, polycyclic aromatic hydrocarbon (PAH)
beta-BHC	21	Las Vegas Wash at Pabco Road	EDC, pesticide[d]
Bisphenol A	2.4	Las Vegas Bay	EDC, plasticizer
Butylbenzylphthalate	900	Las Vegas Creek	EDC, phthalate
Caffeine	660	Sloan Channel	Personal care product, stimulant
Carbamazepine	180	Las Vegas Wash at Pabco Road	Pharmaceutical, antiepileptic
Carisoprodol	Qualitative	Las Vegas Bay	Pharmaceutical, muscle relaxant
Chloroform	1500	Meadows Detention Basin	Disinfection byproduct
Cimetidine	63	Las Vegas Wash below Lake Las Vegas	Pharmaceutical, histamine H 2-receptor antagonists (stomach acid reducer)
Clarithromycin	3	Las Vegas Wash below Lake Las Vegas	Pharmaceutical, antibiotic
Codeine	17 - 123	Las Vegas Bay	Pharmaceutical, narcotic analgesic
Cotinine	130	Las Vegas Wash below Lake Las Vegas	Personal care product metabolite, metabolite of nicotine (stimulant)
DDT	20	Las Vegas Wash at Pabco Road	EDC, pesticide
DEET (or N-N-diethyltoluamide)	383	Las Vegas Wash at Pabco Road	Personal care product, insect repellant
Dehydronifedipine	10	Las Vegas Wash below Lake Las Vegas	Pharmaceutical metabolite, metabolite of nifedipine (hypertension medication)
Di(2-ethylhexyl)phthalate	4650	Las Vegas Creek	EDC, phthalate
Diazepam	3 - 62	Las Vegas Bay	Pharmaceutical, tranquillizer
Diclofenac	7.4	Las Vegas Wash at Pabco Road	Pharmaceutical, analgesic
Phenytoin (Dilantin)	53 - 261	Las Vegas Bay	Pharmaceutical, antiepileptic
Diltiazem	7	Las Vegas Wash below Lake Las Vegas	Pharmaceutical, antihypertensive
Di-n-butylphthalate	700	Meadows Detention Basin	EDC, phthalate
Erythromycin	184	Las Vegas Wash below Lake Las Vegas	Pharmaceutical, antibiotic
Erythromycin - H_20	210	Las Vegas Wash at Pabco Road	Pharmaceutical metabolite, metabolite of erythromycin (antibiotic)
Estradiol	2.4[a]	Maximum LVB 6.7	EDC, hormone
17ß-Estradiol (E2)	2.67	Las Vegas Wash	EDC, hormone
Estriol	17	Las Vegas Wash at Pabco Road	EDC, hormone
Estrone	36	Las Vegas Wash at Pabco Road	EDC, hormone
Ethinylestradiol (EE2)	0.52	Las Vegas Bay	Pharmaceutical & EDC, synthetic hormone
Fluoxetine	12	Las Vegas Wash at Pabco Road	Pharmaceutical, antidepressant
Galaxolide (HHCB)	1093	Las Vegas Wash at Pabco Road	Personal care product, polycyclic musk
Gemfibrozil	271	Las Vegas Wash at Pabco Road	Pharmaceutical, lipid-lowering agent (antihyperlipidaemic)

Table K-1 Maximum Concentrations of Detected PPCPs and EDCs in Surface Water Samples Collected From Las Vegas Wash and Its Tributaries and Las Vegas Bay of Lake Mead.*

Chemical	Maximum Conc. (ng/L)	Sample Location	Chemical Description
Griseofulvin (Fulvicin)	Qualitative	Las Vegas Bay	Pharmaceutical, antifungal agent
Guaifenesin	21 - 52	Las Vegas Bay	Pharmaceutical, expectorant
Heptachlor	13	Las Vegas Wash at Pabco Road	EDC, pesticide
Homomenthyl salicylate	Qualitative	Las Vegas Bay	Personal care product, sunscreen agent
Hydrocodone	104	Las Vegas Wash at Pabco Road	Pharmaceutical, narcotic analgesic
Ibuprofen	37	Las Vegas Wash at Pabco Road	Pharmaceutical, analgesic
Iopromide	253	Las Vegas Wash at Pabco Road	Pharmaceutical, X-ray contrast media
Lead	18,000	Las Vegas Wash @ Northshore Dr (CL3)	EDC, metal
Lindane (gamma-BHC)	180	Kerr-McGee Seeps	EDC, pesticide
Meprobamate	440	Las Vegas Wash at Pabco Road	Pharmaceutical, anti-anxiety medication
Mequinol	Qualitative	Las Vegas Bay	Personal care product, used to treat skin darkened by the sun
Mercury	200	LW6.05	EDC, metal
Methocarbamol	Qualitative	Las Vegas Bay	Pharmaceutical, muscle relaxant
Musk Ketone	167	Las Vegas Wash at Pabco Road	Personal care product, nitromusk
Naproxen	99	Las Vegas Wash at Pabco Road	Pharmaceutical, analgesic
Nicotine	5 - 23	Las Vegas Bay	Personal care product, stimulant
Nonylphenol (NP)	1140	Las Vegas Wash	EDC, degradate of NPE (nonionic surfactants)
Nonylphenol polyethoxylates (NPE)	8990	Las Vegas Wash	EDC, nonionic surfactants
Octylphenol (OP)	43	Las Vegas Wash	EDC, degradate of nonionic surfactants
Oxybenzone	30 - 364	Las Vegas Bay	Personal care product, sunscreen agent
para-Chloroaniline	Qualitative	Las Vegas Bay	EDC, production intermediate and degradation product [c]
Pentoxifylline	5 - 50	Las Vegas Bay	Pharmaceutical, blood thinner
Phenobarbitol	11 - 39	Las Vegas Bay	Pharmaceutical, sedative and anticonvulsant
Primidone	11 - 130	Las Vegas Bay	Pharmaceutical, antiepileptic
Progesterone	44	Confluence of Las Vegas Wash and Lake Mead	EDC, hormone
Pyrene	14	Las Vegas Wash at Pabco Road	EDC, polycyclic aromatic hydrocarbon (PAH)
Sulfamethoxazole	318	Las Vegas Wash at Pabco Road	Pharmaceutical, antibiotic
TCEP	354	Las Vegas Wash at Pabco Road	Personal care Product, flame retardant (not applied to body but to clothing)
Testosterone	1.5	Las Vegas Wash at Pabco Road	EDC, hormone
Triclosan	241	Las Vegas Wash at Pabco Road	Personal care product, antimicrobial agent
Trimethoprim	98	Las Vegas Wash below Lake Las Vegas	Pharmaceutical, antibiotic
Vanillin	Qualitative	Las Vegas Bay	Personal care product, flavoring agent

Conc. = Concentration; TCEP= tris(2-chloroethyl) phosphate; HHCB= hexahydrohexamethylcyclopentabenzopyran; BHC= benzene hexachloride, or hexachlorocyclohexane (HCH); DDT=dichlorodiphenyltrichloroethane.

*Chemicals not detected (with detection or reporting limit, in ng/L, if provided) include: alpha-BHC (<10), alpha-chlordane (<10), aldrin (<10), amoxicillin, anthracene (<10), azithromycin, cadmium (<2000), cephalexin, delta-BHC (<10), chrysene (<10), DDD (<10), DDE (<10), dieldrin (<10), digoxigenin (<8), digoxin (<260), diphenhydramine, enalaprilat (<152), endrin (<10), furosemide, gamma-chlordane (lindane) (<10), heptachlor epoxide (<10), lisinopril, metolachlor (<10), metformin (<3), methoxychlor (<10), miconazole, mirex (<10), paroxetine metabolite (<260), ranitidine (<10), salbutamol (albuterol; <29), thiabendazole, urobilin, and warfarin (<1).

a Assuming that estradiol is the same as 17ß-estradiol, the maximum concentration of estradiol is 2.67 ng/L.

b Personal care product, solvent used to create fragrances, intermediate in production of pharmaceuticals, agrochemicals, and other organic chemicals.

c Intermediate in the manufacture of dyes, pigments, agricultural chemicals and pharmaceuticals; persistent environmental degradate of some herbicides and fungicides.

d BHC(mixture) is a potential EDC, and beta-BHC is a component of this mixture.

Sources: Boyd and Furlong 2002; Snyder et al. 1999; Snyder et al. 2001; Vanderford et al. 2003, Zhou et al. 2004; Nevada DEP, http://ndep.nv.gov/bwqp/cl3amtls.xls; SNWA monitoring data (Shane Snyder, personal communication; March 2006).

Table K-2 Concentrations of EDCs or PPCPs Detected in Tertiary-treated Effluent Collected From an Anonymous Municipal WWTP in the Las Vegas Valley.

EDC/PPCP	Concentration (ng/L)
Acetaminophen	1.6
Androstenedione	1.5
Atrazine	1
Caffeine	29
Carbamazepine	129
DEET (or N-N-diethyltoluamide)	383
Diazepam	2.3
Diclofenac	3.3
Dilantin	106
Erythromycin	51
Estradiol	<1
Estriol	7.8
Estrone	20
Ethinylestradiol	<1
Fluoxetine	<1
Galaxolide (HHCB)	395
gamma-BHC (Lindane)	<10
beta-BHC*	11
Gemfibrozil	5.7
Hydrocodone	68
Ibuprofen	5.6
Iopromide	4.6
Meprobamate	424
Mirex	<10
Musk ketone	37
Naproxen	5.1
Oxybenzone	<1
Pentoxyfylline	<1
Sulfamethoxazole	187
TCEP	354
Testosterone	1.1
Triclosan	4.1
Trimethoprim	6.6

Notes:

Data are taken from Trenholm *et al.* (unpublished manuscript). The data describe concentrations of contaminants detected in tertiary-treated effluent from one of the area municipal WWTP. The specific WWTP is not identified.

TCEP= tris(2-chloroethyl) phosphate;
HHCB= hexahydrohexamethylcyclopentabenzopyran; BHC= benzene hexachloride, or hexachlorocyclohexane (HCH). *BHC (mixture) is a potential EDC, and beta-BHC is a component of this mixture.

Table K-3. Comparison of Maximum Detected Pharmaceutical Concentrations in the Las Vegas Wash or Lake Mead and Water Concentrations Equivalent to the Therapeutic Dose and Other Values.

Drug	Maximum-Detected Water Conc. (µg/L)	Minimum Therapeutic Dose (mg/d)	Equivalent Drinking Water Conc. (µg/L) h	Equivalent Drinking Water Conc./1000 (µg/L)	Versteeg et al. PDWL (µg/L) [i]		Margin of Safety Relative to Therapeutic Dose/1000	Margin of Safety Relative to Versteeg et al. PDWL
Acetaminophen	0.051	160 [a]	560,000	560	NA		11,000	NA
Caffeine	0.66	NA	NA	NA	1500		NA	2,300
Carbamazepine	0.18	10 [b]	35,000	35	50		190	280
Cimetidine	0.063	200 [c]	101,500	100	NA		1,600	NA
Clarithromycin	0.003	500 [c]	248,500	250	NA		83,000	NA
Codeine	0.123	16 [c]	8,050	8.1	NA		66	NA
DEET	0.4	NA	NA	NA	NA		NA	NA
Dehydronifedipine	0.01	30 [c]	15,050	15	NA		1,500	NA
Diazepam	0.062	2 [c]	1,015	1	NA		16	NA
Diclofenac	0.0074	100 [c]	49,000	49	7.5		6,600	1,000
Dilantin	0.261	100 [d]	350,000	350	NA		1,300	NA
Diltiazem	0.007	120 [c]	59,500	60	NA		8,600	NA
Erythromycin	0.184	300 [d]	1,050,000	1100	15		6,000	82
Erythromycin - H20	0.210	300 [d]	1,050,000	1100	15		5,200	71
Ethinylestradiol (EE2)	0.00052	0.005 [c]	2.7	0.0027	NA		5.2	NA
Fluoxetine	0.012	10 d	1,400,000	1400	NA		120,000	NA
Gemfibrozil	0.271	1200 [c]	595,000	600	NA		2,200	NA
Guafenesin	0.052	400 [c]	199,500	200	NA		3,800	NA
Hydrocodone	0.104	30 [c]	15,050	15	NA		140	NA
Ibuprofen	0.037	50 [e]	350,000	350	150		9,500	4,100
Iopromide	0.253	NA	NA	NA	NA		NA	NA

Table K-3. Comparison of Maximum Detected Pharmaceutical Concentrations in the Las Vegas Wash or Lake Mead and Water Concentrations Equivalent to the Therapeutic Dose and Other Values (Continued).

Drug	Maximum-Detected Water Conc. (µg/L)	Minimum Therapeutic Dose (mg/d)	Equivalent Drinking Water Conc. (µg/L) [h]	Equivalent Drinking Water Conc./1000 (µg/L)	Versteeg et al. PDWL (µg/L) [i]		Margin of Safety Relative to Therapeutic Dose/1000	Margin of Safety Relative to Versteeg et al. PDWL
Meprobamate	0.440	200 [f]	220,500	220	NA		500	NA
Naproxen	0.099 [d]	125	455,000	460	NA		4,600	NA
Oxybenzone	0.364	NA	NA	NA	NA		NA	NA
Pentoxifylline	0.050	800 [c]	385,000	390	NA		7,800	NA
Phenobarbitol	0.039	125 [c]	63,000	63	NA		1,600	NA
Primidone	0.13	50 [c]	24,850	25	NA		190	NA
Sulfamethoxazole	0.318	400 [g]	2,800,000	2800	75		,8800	240
Triclosan	0.241	NA	NA	NA	NA		NA	NA
Trimethoprim	0.098	80 [d]	280,000	280	NA		2,900	NA

Notes:

[a] Dose recommended for a child, age 2-3 years; body weight of 10 kg assumed.

[b] Dose recommended for a child, age less than 6 years; body weight of 10 kg assumed.

[c] Dose recommended for an adult; body weight of 70 kg assumed.

[d] Dose recommended for a "child" or "pediatric" ; body weight of 10 kg assumed.

[e] Dose recommended for a child, age 6-12 months; body weight of 5 kg assumed.

[f] Dose recommended for a child, age 6-12 years; body weight of 32 kg assumed.

[g] Dose recommended for a child, age greater than 2 months; body weight of 2 kg assumed.

[h] Calculated by first estimating the minimum therapeutic dose in mg/kg-day, based on the subject's assumed body weight, then multiplying the dose by an assumed adult body weight of 70 kg, dividing by an assumed drinking water ingestion rate of 2 L/day, and multiplying by a conversion factor of 1,000 (µg/mg).

[i] PDWL = Provisional Drinking Water Limit.

These ongoing studies are also examining the potential cumulative effects of trace levels of pharmaceuticals that act on the same biological endpoint. Although toxicologists are beginning to examine schemes by which to evaluate hazards from chemical mixtures, toxicological understanding in this area is in its early stages. It is known that pharmaceuticals and other chemicals, when administered together, can influence the toxicity of one another. For example, a chemical may block the access of another to a biological receptor, and thus reduce the overall activity of the second compound. In other cases, a chemical may act to increase the relative activity of another. Predicting these types of effects is difficult, however, since interactions are expected to change depending on the composition and relative concentrations of compounds in a mixture, and it is impossible to test all possible combinations. Nonetheless, it is expected that very low level exposures to multiple compounds are not a concern in this regard, if exposures are at levels below the lowest doses at which the compounds are "biologically active."

Some potential effects of pharmaceuticals are difficult to predict. For example, some pharmaceuticals (e.g., antibiotics) are known to cause allergic reactions in humans, but predicting the likelihood of eliciting allergic effects at very low doses is difficult, because when people become sensitized to the compound, they can respond to it at extremely low levels of exposure. The possibility of microbial resistance induced by antibiotics in the environment is a subject that remains controversial. Microbial resistance to antibiotics has been noted in surface water and sewage effluent. Ayscough et al. (2000) concluded that the most likely cause is not the induction of resistance caused by exposure to low levels of antibiotics, but the excretion of resistant organisms by humans and animals receiving antibiotic treatment.

K.2.2 EDCs

Toxicity assessments for EDCs are complicated by a number of factors. Endocrine disrupting chemicals can act at multiple sites in the body and through many mechanisms. For example, some EDCs bind to hormone receptors, while others affect hormone synthesis, transport, metabolism, and distribution. While much is known about the early molecular events involved in hormone response, relatively little is known about the potential for changes in hormone responses to result in adverse effects in an organism. Internal homeostatic controls on the endocrine system can sometimes compensate for the effects of EDC exposure such that no adverse effect results. However, different life stages of the same organism might be affected by the same EDC in different ways. For example, while the homeostatic controls in an adult organism might readily adjust for changes caused by EDC exposure and prevent adverse consequences, a developing organism of the same species might be permanently and severely affected by the same dose. Exposures that occur during sensitive periods of development might result in apparent adverse effects only when the exposed organism reaches adulthood or attempts to reproduce (WHO 2002).

Humans and organisms in the environment are exposed to mixtures of EDCs rather than to individual chemicals. It is possible for simultaneous exposure to multiple EDCs in a mixture to produce an additive effect on an endocrine system, or one chemical might increase (synergism) or decrease (antagonism) an organism's response to concurrent EDC exposure. Although the EPA recommended that common mixtures of EDCs should be screened for endocrine activity, they also determined that screening of mixtures for endocrine activity should be deferred until EPA is confident in its screening methods for individual chemicals (EPA 2005b). The picture is further complicated by the fact that

there are multiple mechanisms by which EDCs could affect the functioning of a single endocrine system and that interactions among the different endocrine systems can occur (WHO 2002).

Controversy surrounding the assignment of the label "EDC" to a chemical stems in part from the lack of a consistent definition. Some definitions include chemicals for which the only evidence of endocrine activity is an effect at the molecular or cellular level (e.g., receptor binding assay, in vitro cellular bioassay). Others use a qualifier such as "potential" or "putative" to describe such a chemical and require demonstration of an adverse effect in an intact organism (in vivo) to designate a chemical as an EDC. In most cases where adverse effects have been reported to be associated with EDC exposure, the mechanism by which the effects occurred is poorly understood, making it difficult to conclude that a causal relationship exists between exposure and effect.

Historically, the adverse effects of diethylstilbestrol (DES), a medication once prescribed to pregnant women, on the children exposed during gestation have clearly demonstrated that humans are susceptible to the effects of EDCs. However, DES was a drug intentionally administered and ingested at high doses. Doses of EDCs that might be accrued from typical environmental exposures or to trace concentrations of EDCs in drinking water are expected to be quite small by comparison. Based on the available information, Ayscough et al. (2000) concluded that the only pharmaceutical for which subtle endocrine disrupting effects have been currently demonstrated in laboratory studies at environmentally relevant concentrations is EE2. Human and animal studies of the effects of long-term exposures to environmentally-relevant doses are unavailable for most potential EDCs, but certain studies, some of which are controversial, indicate that a few EDCs can cause effects at very small doses. Industrial chemicals, organochlorine pesticides, and naturally occurring chemicals have been implicated as potential causes for a suite of effects reported in humans, but specific chemical causes have not been established, and in some cases, the existence of the effects has been disputed.

The International Programme on Chemical Safety (IPCS) conducted an assessment of the state-of-the-science for endocrine disruptors (WHO 2002) that provided the following conclusions with regard to potential effects of EDCs on human health.

"Although it is clear that certain environmental chemicals can interfere with normal hormonal processes, there is weak evidence that human health has been adversely affected by exposure to endocrine-active chemicals… Generally, studies examining EDC-induced effects in humans have yielded inconsistent and inconclusive results, which is responsible for the overall data being classified as "weak." This classification is not meant to downplay the potential effects of EDCs; rather, it highlights the need for more rigorous studies…The only evidence showing that humans are susceptible to EDCs is currently provided by studies of high exposure levels. Our understanding of the effects of chronic, low levels of EDCs are much more obscure. In particular, the relationship between early-life exposures to EDCs in humans and functioning in adult life is poorly understood. This is a concern because laboratory animal studies have indicated that early life stages may be especially sensitive to the effects of EDCs. Only recently have human epidemiological studies been conducted with the necessary rigor to sufficiently address potential cause-and-effect relationships in regards to EDC exposures."

"Analysis of human data by itself, while generating concerns, has so far failed to provide firm evidence of direct causal associations between low-level (i.e., levels measured in the general population) exposure to EDCs and adverse health outcomes."

"Overall, the biological plausibility of possible damage to certain human functions (particularly reproductive and developmental systems) from exposure to EDCs seems strong when viewed against the background of known influences of endogenous and exogenous hormones on many of these processes. Furthermore, the evidence of adverse outcomes in wildlife and laboratory animals exposed to EDCs substantiates human concerns. The changes in human health trends in some areas (for some outcomes) are also sufficient to warrant concern and make this area a high research priority, but non-EDC mechanisms also need to be explored."

According to Anderson (2005), "Large studies have not indicated any association with a list of effects that have sometimes been attributed to environmental exposure to EDCs: low sperm counts, premature puberty in girls, testicular cancer in young men, and breast cancer in some women." Assessments of the potential for effects in humans due to exposure to EDCs in wastewater and reuse water also have not indicated a risk. Studies evaluating the health effects of using treated wastewater for groundwater recharge in Los Angeles County showed that after nearly 30 years of recharge, there is no association between exposure to reuse water and cancer rates, mortality, infectious disease, or adverse birth outcomes including effects on prenatal development, infant mortality, and birth defects (EPA 2004). Similarly, Anderson (2005) concluded that no studies to date have effectively linked low concentrations of EDCs in wastewater to adverse effects in people.

K.3 Potential EDC/PPCP Exposures and Effects on Fish

Fish and other aquatic organisms are expected to receive much greater exposure than humans to EDCs and PPCPs in the aquatic environment. Fish are constantly immersed in water and can bioconcentrate waterborne contaminants by direct uptake from water across the gill. Fish also can be exposed to lipophilic contaminants through diet or exposure to contaminated sediment or suspended particulate material. Humans are likely to receive much less exposure to wastewater-derived contaminants by these routes. In oligotrophic to mesotrophic water bodies like Lake Mead, fish often congregate near municipal wastewater discharges where increased nutrient input can result in greater availability of food and plant cover. This behavior also results in greater exposure to wastewater-related contaminants. While people are exposed intermittently to waterborne contaminants, fish may be exposed continuously and are more likely to be exposed during critical periods of development when organisms are most sensitive to the effects of contaminants.

While evidence that widespread endocrine disruption is occurring among humans exposed to commonly encountered concentrations of EDCs is weak, there is substantial evidence that EDCs and PPCPs at levels found in WWTP effluents can cause endocrine disruption in fish. Studies conducted in Europe (Jobling et al. 1998, Harries et al. 1997, Rodgers-Gray et al. 2001, Routledge et al. 1998), Canada (Schoenfuss et al. 2002), the United States (Hemming et al. 2001), and elsewhere have reported estrogenic effects in fish due to exposure to municipal and industrial WWTP effluents. Because WWTP effluents contain complex mixtures of EDCs and PPCPs, most of these studies have been unable to pinpoint the specific chemicals that are responsible for the observed effects, but likely causative agents include the animal hormones 17β-estradiol (E2) and estrone, the pharmaceutical EE2, and in some cases nonylphenol (NP) and octylphenol (OP).

Several studies of EDC occurrence and ecological effects have been conducted in the Boulder Basin of Lake Mead, which receives a significant input of tertiary treated effluent from the Las Vegas Wash. Various locations in the Las Vegas Wash and Boulder Basin including the Las Vegas Bay were investigated between 1992 and 2001. Target aquatic species included the common carp

(Cyprinus carpio), the largemouth bass (Micropterus salmoides), and the endangered razorback sucker (Xyrauchen texanus). Target compounds included pesticides, PCBs, semivolatile industrial compounds, alkylphenols, polycyclic aromatic hydrocarbons (PAHs), polychlorinated dibenzo-p-dioxins, polychlorinated dibenzofurans, and steroid hormones. The focus of this discussion will be on those studies published in the peer-reviewed literature.

From 1992 to 1995, Bevans et al. (1996) investigated the occurrence of organochlorines and semivolatile industrial compounds in the water column, bottom sediment, and common carp tissue collected from the Las Vegas Wash and Boulder Basin of Lake Mead. The study used semi-permeable membrane devices (SPMDs) to identify contaminants in the water column. The SPMDs did not allow for determination of waterborne concentrations of the contaminants under study but rather were used to make comparisons of the relative degree of contamination among sites of interest. In addition, the researchers assessed the endocrine status of carp by analyzing blood plasma concentrations of the sex steroid hormones E2 and 11-ketotestosterone (11-KT) and the estrogen-inducible egg-yolk-protein precursor vitellogenin (VTG). Elevated plasma or serum VTG in male fish is used as a biomarker of exposure to estrogen-like (estrogenic) chemicals, as this protein usually is produced in appreciable amounts only in female fish and has no known function in males. Histology of carp gonads and other organs also was examined for evidence of effects that might result from exposure to EDCs.

The investigators reported that carp collected from Las Vegas Wash and Las Vegas Bay (as compared to those from reference location Callville Bay) demonstrated effects indicative of endocrine disruption, including elevated blood-plasma concentrations of 11-KT (an androgen, or male hormone) in female carp in Las Vegas Wash and depressed plasma 11-KT and E2 in male carp from Las Vegas Bay. It has been suggested that the ratio of E2:11-KT in the blood typically is less than 1 in male fish and greater than 1 in female fish and that deviations indicate endocrine disruption. Half of the female carp from Las Vegas Wash had plasma E2:11-KT ratios less than 1 (similar to males), while ratios of plasma E2:11-KT generally were normal for male and female carp from Las Vegas Bay and Callville Bay. According to Bevans et al. (1996), the most compelling evidence of endocrine disruption in carp was the presence of high levels of VTG in blood plasma of male carp collected from Las Vegas Wash and Bay, as well as elevated concentrations in female carp from Las Vegas Bay. Elevated VTG suggests that these fish were exposed to an estrogenic EDC. However, the normal appearance of the histology of all gonad samples and similar degree of sexual maturity among carp of the same sex among the sampling sites indicates that the effects did not result in damage to gonad tissue structure. Slight necrotic changes observed in carp hetapopancreas and kidney samples from all sampling locations (including the reference location) were reported to be consistent with long-term subchronic exposure to toxicants (Bevans et al. 1996).

Bevans et al. (1996) reported that SPMDs (which sample waterborne contaminants), sediment, and carp tissue from Las Vegas Wash and Las Vegas Bay contained elevated levels of known or suspected EDCs relative to the reference location. More details on contaminants detected in SPMDs are provided in the discussion of the report by Tuttle and Orsak (2002) below. The investigators concluded that the endocrine disruption they observed in carp from Las Vegas Wash and Las Vegas Bay could be due to the presence of organochlorine compounds and semivolatile industrial compounds detected in environmental samples from those locations. Many of the detected contaminants have been reported to be associated with endocrine disruption. Dichlorodiphenyltrichloroethane (and/or its metabolite DDE), PCBs, and PAHs have been associated with possible endocrine disruption resulting in reduced reproductive success in fish, though non-endocrine modes of action have not been discounted (WHO 2002). However, benchmark concentrations of these contaminants in sediment or

fish tissue that are known to cause endocrine disruption, or that are known to be less than levels that cause endocrine disruption, in fish currently are unavailable.

In response to the 1996 report, additional studies were initiated to confirm evidence of endocrine disruption and to attempt to identify EDCs in water samples collected from the Las Vegas Wash and Bay. Large-volume water extraction and mass spectrometry were used in 1998 and 1999 to measure waterborne concentrations of estrogenic EDCs (Snyder et al. 1999). Estrogenic EDCs that were detected included EE2 (active estrogenic ingredient in oral contraceptive medication); the hormone E2; and NP, OP, and nonylphenol ethoxylates (NPE), all of which are estrogenic degradation products of the widely used nonionic alkylphenol polythoxylate surfactants used in several personal care products and in other applications. These compounds were found in the Las Vegas Wash and Las Vegas Bay, but were not detected at other locations in the Boulder Basin (Snyder et al. 1999). EE2 and E2 were not detected using conventional analytical instruments but were detected in the Las Vegas Wash and Las Vegas Bay using radioimmunoassay.

Snyder et al. (2001) then used an estrogen-responsive cell bioassay in combination with analytical chemistry techniques in a bioassay-directed fractionation and identification scheme designed to identify estrogenic EDCs of greatest bioactivity in water samples collected from the Las Vegas Wash and Boulder Basin of Lake Mead. The investigators concluded that E2 and EE2 were the dominant estrogenic EDCs in these waters. Results of in vitro cellular bioassays are not always predictive of in vivo effects such as those reported in Lake Mead carp, and it is premature to infer that exposure to EE2 and E2 are solely responsible for estrogenic effects observed in feral fish from the Las Vegas Wash and Las Vegas Bay. However, laboratory studies have shown that small concentrations of E2 and EE2 can induce estrogenic effects in fish (Purdom et al. 1994, Länge et al. 2001, Nash et al. 2004, Sumpter and Johnson 2005).

Further investigations of common carp from Lake Mead were begun in 1999 in an attempt to confirm evidence of endocrine disruption in vivo as well as to account for some difficulties in interpreting results of the previous work. One of the difficulties in identifying the potential chemical cause(s) for the effects reported in fish from Las Vegas Wash and Las Vegas Bay is the lack of an entirely suitable reference site. Differences in general water quality parameters/or habitat between the Las Vegas Wash and Las Vegas Bay and potential reference sites within Lake Mead tend to confound the results of site comparisons. In particular, water temperature has a strong influence on timing of reproduction and associated changes in reproductive physiology of carp. Differences in water temperature and other factors such as food availability can result in differences among fish at various locations with regard to reproductive timing and status and associated endpoints used to assess endocrine disruption. Carp reproductive status varies over the course of a year, and effects of EDCs might be more readily detected at certain periods during the reproductive cycle. Fish from different sites, then, must be in similar stages of reproductive development (or expected to be) to draw appropriate conclusions regarding potential differences due to EDC exposure.

Patiño et al. (2003) conducted a seasonal study of carp collected from two locations in Lake Mead, one in the general area of the Las Vegas Bay (more contaminated site) and one on the Overton Arm of Lake Mead (less contaminated site). The sampling period included two spawning seasons. The investigators reported that male carp showed similar patterns of seasonal changes in gonadal development between these sites, but male carp from Las Vegas Bay consistently had less-developed gonads and, during one sampling event, a lower proportion of fully developed sperm. Female carp demonstrated differences in reproductive timing between locations that appeared to follow differences

in water temperature profiles. For female carp, estimates of fecundity based on development of oocytes (unovulated eggs) in the gonads indicated that females from the Overton Arm produced a smaller number of fully developed oocytes and might have failed to spawn during the second spawning season. The reason for this difference is not clear but the investigators proposed that this might be related to relatively inferior nutritional status of fish from the Overton Arm. Fish from Las Vegas Bay generally were longer and heavier than fish from the Overton Arm, indicating better nutritional status for the former. The investigators concluded that environmental contamination was the only variable that could explain differences in gonadal development between males at different locations, while the differences between females at the two locations were likely due to differences in water temperature and nutritional status of the fish.

Little is known about the potential for common carp to move among the various locations where the fish have been collected for endocrine disruption studies in Lake Mead. As a result, there is some question whether effects observed in the fish are truly related to contaminant exposure received at the locations where the fish were collected. Holding fish in cages at the locations of interest ensures that observed differences among locations are site-related, though it does not ensure that chemical exposure is the only site-related variable that might explain differences in endocrine endpoints. In such a "caged fish" study, site-related differences in temperature and other water quality parameters and availability of natural food remain, but it is simpler to assess the temperature differences because the fish are held in one location that can be more readily monitored.

In late winter to early spring of 1999, Snyder et al. (2004) placed farm-raised adult male and female common carp in cages at four locations in the Boulder Basin of Lake Mead. Sites included Las Vegas Wash, Las Vegas Bay, Moon Cove (reference site 1), and Water Barge Cove (reference site 2). Two reference sites were used because previous studies suggested that this approach aids in accounting for differences in reproductive timing and other site-related differences not related to contamination that can confound the results of endocrine disruption studies in fish. Fish were held in cages for 42 to 48 days. Endpoints that were examined included gonad development and histology, profiles of blood plasma concentrations of sex steroids (testosterone [T], E2, 11-KT) and VTG, steroidogenic potential of gonad tissue, and induction of hepatic xenobiotic biotransformation enzymes. It is important to note that the fish in this study were not exposed to bottom sediment and were not exposed to contaminants in the Las Vegas Wash or Las Vegas Bay for the entire duration of their life-cycle, as feral fish might be.

There were no significant differences in gonad development or histology among carp held at different locations. Slightly greater plasma VTG in male carp held in the Las Vegas Wash compared to those at the other exposure sites and modest elevation in plasma E2 in male carp held at Las Vegas Wash and Las Vegas Bay might indicate exposure to estrogenic contaminants, but causes other than contaminant exposure (such as site-related temperature differences) cannot be discounted. Slight elevation in plasma VTG is not considered to be an adverse effect. There were no differences in plasma T concentrations or in ratios of plasma estrogen to androgens among male fish at different sites and no significant differences in plasma 11-KT concentrations among male fish at Las Vegas Wash, Las Vegas Bay, and one reference site (Water Barge Cove). There were no differences in plasma 11-KT among female carp at different sites, and no differences in plasma E2 among female carp at Las Vegas Wash, Las Vegas Bay, and one reference site (Moon Cove). There were differences in plasma T among females at different locations, but the differences did not appear to be related to exposure to the flow of the Las Vegas Wash. No differences in plasma E2:11-KT ratios were observed among female carp at Las Vegas Wash, Las Vegas Bay, and one reference site (Moon Cove). Female carp held at

Las Vegas Wash had elevated plasma E2:T ratios compared with those at the other three sites; this could indicate that these fish were in a less advanced stage of reproductive development, possibly due to contaminant exposure, or it might indicate slight site-related differences in reproductive timing that are unrelated to contaminant exposure (Snyder et al. 2004).

Gonad tissue taken from both male and female carp held at Las Vegas Bay showed greater basal capacity to produce T than did tissue taken from carp held at the other sites (which is opposite what generally would be expected for an endocrine disrupter effect), but this did not result in greater blood plasma levels of T in these fish relative to those at both reference sites. Gonad tissue taken from female carp held at Las Vegas Wash had less capacity to produce T than did tissue from females at other sites, but this did not result in significantly reduced sex steroid levels in the blood plasma. Measurements of the activity of a certain enzyme in the hepatopancreas indicated that dioxin-like contaminants did not have a substantial effect on the caged carp, and the small elevation in enzyme activity observed in fish held in the Las Vegas Wash might have been related to the elevated water temperature at that site relative to the other sites. The investigators reported that few differences among fish caged at different locations were potentially attributable to contaminant exposure in the Las Vegas Wash and Las Vegas Bay. Water temperature differences among locations complicated interpretation of the results. Variation in some endpoints between carp at the two reference locations supports the use of multiple reference sites in these types of studies. For a brief comparison of the results of various studies of potential endocrine disruption in Lake Mead carp (see Snyder et al. 2004).

In 1998, the U.S. Geological Survey (USGS) Biological Resources Division and the U.S. Fish and Wildlife Service (USFWS) initiated a cooperative effort to assess contaminants associated with the Las Vegas Wash and potential effects on fish and wildlife. The investigation was expanded in 2000 and field data were collected in 2001. The following were the objectives of the USFWS.

1) Review existing data to assess the existence and degree of threats to fish and wildlife,

2) Assess organochlorine compounds and trace elements in bird eggs,

3) Assess razorback sucker (*Xyrauchen texanus*) exposure to endocrine disrupting compounds and other contaminants, and

4) Assess the potential for downstream impacts to endangered fishes and critical habitat.

The results of the USFWS portion of this expanded effort are reported by Tuttle and Orsak (2002). Our review of the USFWS report emphasizes the occurrence of EDCs and PPCPs and their potential effects on fish, including the razorback sucker.

The razorback sucker was once abundant throughout the Colorado River and its major tributaries but is now endangered. The primary reasons for its decline are changes in biological and physical features of its habitat. Predation of larval razorback suckers by non-native species is an important contributing factor to the decline of this species, and environmental contaminants might play a role in poor recruitment in some areas. Two populations of razorback suckers occur in Lake Mead—one at Echo Bay on the Overton Arm and one in the Las Vegas Bay. Razorback suckers occur throughout Las Vegas Bay and have been found in the lower Las Vegas Wash, and they are believed to spawn in the vicinity of Blackbird Point in Las Vegas Bay. The USFWS is particularly concerned about potential effects of contaminants, especially EDCs, associated with the Las Vegas Wash on this species (Tuttle and Orsak 2002).

To address objective (3) above, USFWS began a study to assess exposure of razorback suckers to EDCs and other contaminants in the Las Vegas Wash and to evaluate potential implications to survival and reproduction. Two frozen whole razorback suckers (one adult from Blackbird Point in Las Vegas Bay and one juvenile from Echo Bay) were opportunistically obtained when these fish died during a telemetry study conducted by a private consultant. Whole fish were analyzed for the presence of trace elements and organochlorine compounds. The investigators reported that 9 of 22 analyzed organochlorine compounds were detected in the razorback sucker collected from the Las Vegas Bay, while none of these contaminants were detected in the razorback sucker from Echo Bay. DDT residues (DDT and metabolites DDE and DDD) accounted for more than half of the total detected organochlorines in the Las Vegas Bay razorback sucker, while total PCBs accounted for about a third (Tuttle and Orsak 2002).

Comparisons made between the concentrations of contaminants in the fish from these two locations should be viewed with extreme caution because the number of samples is small (one from each location) and there is great disparity in body size and age. Larger, older fish often contain greater concentrations of contaminants than smaller, younger fish (WSDOH 2005). Likewise, comparisons that were made between concentrations of contaminants in razorback suckers and carp should be considered with skepticism because of the small sample sizes; potential species-dependent differences in contaminant uptake, metabolism, and excretion; and lack of information regarding the ages and sizes of the carp; and differences in the tissue collection techniques for the two species. Tissue-based criteria for these contaminants to protect fish from endocrine disruption are not available. However, the investigators indicated that tissue concentrations of DDT and PCBs in razorback suckers and carp from the Las Vegas Wash and Las Vegas Bay were less than levels associated with effects to survival, growth, reproduction, biochemical changes, and cellular-level effects (Tuttle and Orsak 2002).

As part of the same study (Tuttle and Orsak 2002), razorback suckers at Las Vegas Bay and Echo Bay (reference site) were caught in trammel nets to evaluate their blood plasma reproductive hormone concentrations and ratios, blood plasma contaminant concentrations, and sperm quality. Because of their endangered status, these fish were not killed for histological examination. Razorback suckers were caught in 2000 and 2001, but results currently are available only for the fish sampled in 2000, which included 11 males and 1 female from Las Vegas Bay and 10 males and 4 females from Echo Bay (reference site). These fish showed no overt external indications of adverse health effects of environmental contaminants, and there were no significant differences in length, weight, or condition factor between males at the two sampling locations. The number of female fish sampled is too small to make statistical comparisons. The investigators report that razorback suckers from Las Vegas Bay exhibited evidence of endocrine disruption. Male fish collected from Las Vegas Bay had higher blood plasma concentrations of E2, lower concentrations of 11-KT (not statistically significant), and greater plasma E2:11-KT ratio than males from Echo Bay. Though sample sizes for female fish were too small to draw any conclusions with confidence, the single female razorback sucker collected from Las Vegas Bay was reported to have lower plasma E2 and E2:11-KT ratio than the females from Echo Bay. The implications to razorback sucker physiology and function are uncertain. Results of blood plasma contaminant concentrations are not yet available, and attempts to assess sperm motility and viability were not successful. The investigators stated that ethinylestradiol was detected in the blood of razorback suckers from Las Vegas Bay and in carp from Las Vegas Bay and Callville Bay, with significantly greater concentrations in those from Las Vegas Bay, but these apparently are preliminary findings and the method of detection and concentrations are not provided. Additional

preliminary findings for common carp and largemouth bass are provided by Tuttle and Orsak (2002) but are not discussed in the current report because the data are not available for evaluation.

The USGS and USFWS joint investigation also included a study that employed SPMDs and common carp to assess the occurrence of contaminants and fish endocrine disruption in the Colorado River downstream of Hoover Dam and in Lake Mohave. Sites that were investigated include Las Vegas Bay, the USGS gauging station on the Colorado River downstream of Hoover Dam, a site near the Willow Beach boat launch area, and a site in Cottonwood Cove on Lake Mohave. In 1998, SPMDs were used to assess the occurrence of selected organochlorine compounds in the water column at these sites. The results were compared with SPMD data collected in 1995 for Las Vegas Wash, Las Vegas Bay, and Callville Bay (Bevans et al. 1996). In 1998, common carp were collected from some of the sites where the SPMDs were placed that same year: Hemenway Beach (n=7), Willow Beach (n=19), and Cottonwood Cove (n=20). Blood and tissue samples were taken from the carp for assessment of endocrine disruption biomarkers, followed by analysis of the carcasses for concentrations of organochlorine pesticides and PCBs. The tissue residue data were compared with similar data for carp collected in 1995 at Las Vegas Wash, Las Vegas Bay, and Callville Bay (Bevans et al. 1996).

The number of detected organochlorine compounds and combined organochlorine concentrations were greatest in SPMDs from Las Vegas Wash, generally less in Las Vegas Bay, and significantly less (not detected) in those from sites downstream of the Hoover Dam (Tuttle and Orsak 2002). The DDT metabolites DDD and DDE comprised approximately one-half of the combined organochlorine concentration, while PCBs comprised about one-quarter. For SPMDs deployed in 1995, the combined concentrations of tetrachlorodibenzo-p-dioxins and tetrachlorodibenzofurans were greatest in SPMDs from the Las Vegas Wash, less in those from Las Vegas Bay, and least in those from Callville Bay (Bevans et al. 1996). PAHs were elevated at all sampling sites (Bevans et al. 1996). Elevated concentrations of perchlorate downstream of the Hoover Dam indicate that some contaminants originating in the Las Vegas Wash can reach the lower Colorado River (Tuttle and Orsak 2002). However, occurrence data obtained with SPMDs suggest that lipid-soluble contaminants did not pass through the Hoover Dam during the sampling period, which coincided with the maximum intrusion of the flow of the Las Vegas Wash into Lake Mead at that time (Tuttle and Orsak 2002).

Of the 13 organochlorine compounds that were detected in carp in 1995 and 1998, the number of detected compounds and the total combined concentrations were greatest in fish from Las Vegas Bay. With the exception of Cottonwood Cove, DDE, DDD, and PCBs accounted for the majority of the total organochlorine residues in carp tissue. While organochlorine compounds were detected in fish in the Colorado River downstream of Hoover Dam and in Lake Mohave, the source(s) of those contaminants have not been identified, and the investigators did not believe that the contaminant levels in the fish posed a significant threat to their reproduction or survival (Tuttle and Orsak 2002).

In general, carp collected downstream of the Las Vegas Wash and Las Vegas Bay were in good condition. Female carp from Hemenway Beach were in significantly better condition than those from Cottonwood Cove. Gonadosomatic index (a measure of gonad size in relation to body weight) was less in male carp from Willow Beach than in males from Hemenway Beach or Cottonwood Cove, possibly due to cooler water temperatures at Willow Beach relative to the other sites resulting in delayed sexual maturation. Assessment of blood plasma E2 and 11-KT concentrations and ratios of E2:11-KT in male and female carp did not reveal significant abnormalities. VTG was not detected in the plasma of either of the two male carp collected from Hemenway Beach (note the small sample

size) but was detected in a few of the male carp from Willow Beach and Cottonwood Cove (Tuttle and Orsak 2002).

Past and ongoing research at Lake Mead has produced unequivocal evidence that EDCs and PPCPs occur in the Boulder Basin of Lake Mead and that some of these contaminants are associated with the Las Vegas Wash. A growing body of evidence suggests that endocrine disruption has been observed in common carp collected from Las Vegas Wash and Las Vegas Bay, but a specific chemical cause has not yet been identified. The sources of potential EDCs and PPCPs to the Las Vegas Wash include tertiary-treated municipal wastewater effluent, contaminated shallow groundwater seeps, urban runoff, and stormwater flows. Any or all of these flows are likely to contain EDCs, but there currently is insufficient information to determine whether these chemicals, either alone or in combination, are present at concentrations great enough to cause the reported effects in fish or to pinpoint their exact source. Pharmaceuticals and personal care products probably are associated to the greatest extent with municipal wastewater treatment plant effluents but also could enter Lake Mead from other sources. For example, pharmaceuticals in excreta from medicated pets and hormones in excreta of pets and wildlife might enter the Las Vegas Wash with irrigation water or stormwater flows, and personal care products could be washed directly into the water from the bodies of swimmers in Boulder Basin. In these cases, the contaminated water enters Lake Mead without the potential benefits of treatment and removal in a WWTP. It is unclear at this time whether altering the volumes or relative volumes or attempting to remove or treat the contaminants present in these constituent flows would change the current endocrine status of fish in Lake Mead.

There is an increasing body of literature describing the effects of waterborne exposure to EDCs and PPCPs on fish and other aquatic life. However, no guidelines, benchmarks, water quality criteria, or "safe" levels of EDCs or PPCPs in wastewater have been developed in the United States for the protection of aquatic life. While surface water criteria and regulations do exist for some chemicals that might be considered to be EDCs, these guidelines or criteria are not based on potential endocrine disruptive effects, but rather on more traditional toxicity testing endpoints used for aquatic life, such as mortality, effects on reproduction, decreased growth, etc. While these test results are useful for identifying concentrations that can cause adverse effects on aquatic life, they often do not address the potential for more subtle, long-term effects of chronic exposure to environmentally relevant concentrations of EDCs and PPCPs. Basing levels of concern on acute or overt effects, which might occur at higher concentrations than would effects occurring through an endocrine-mediated or pharmaceutical mode of action, could lead to over-confidence in the level of protection that they afford. For most EDCs and PPCPs, more information is needed to identify concentrations in water that are protective of aquatic life.

Nonylphenol (NP) is an example of an EDC for which water quality criteria for protection of aquatic life have been developed. NP is an organic chemical used primarily as an intermediate to produce other chemicals such as NPE, which are nonionic surfactants produced and used in large quantities in the United States and elsewhere. NP is moderately soluble and persistent in water and is toxic to aquatic organisms, and is a common contaminant of surface waters. NP in the environment occurs primarily as a result of degradation of NPE by sewage sludge in industrial and municipal WWTP and further transformation of degradates in effluents discharged to the environment. NP has a log KOW of 3.80 to 4.77, indicating that moderate bioaccumulation in aquatic organisms may be expected. However, bioconcentration factors (BCF) and bioaccumulation factors (BAF) for NP suggest that it is metabolized to some extent. Lipid-normalized BCF for freshwater fish ranged from 39 to 209 (EPA 2005b).

The EPA has set ambient water quality criteria for NP for protection of aquatic life. According to EPA (2005b), aquatic life should not be affected unacceptably if the one-hour average concentration of NP does not exceed 28 µg/L more than once every three years on the average (Criteria Maximum Concentration (CMC) or Acute Criterion), and the four-day average concentration of NP does not exceed 6.6 µg/L more than once every three years on the average (Criteria Continuous Concentration (CCC) or Chronic Criterion). To date, the maximum reported concentration of NP in surface water of the Las Vegas Wash or Boulder Basin of Lake Mead is 1140 ng/L (or 1.140 µg/L) for a sample collected from the Las Vegas Wash (Table K-1); this concentration does not exceed the EPA criteria for NP. Several review articles have described the estrogenic (endocrine disruptive) effects of NP, primarily demonstrated by effects on aquatic species using endpoints that do not meet acceptability requirements for data used to derive National Ambient Water Quality Criteria. Hence, this information was not considered in setting the EPA criteria, except to the extent that the effects on these endpoints were integrated into whole organism endpoints such as growth and development that are deemed suitable for deriving the EPA criteria (EPA 2005b).

According to data summarized by EPA (2005b), NP seldom has been reported to induce estrogenic effects at concentrations less than the EPA chronic aquatic criterion of 6.6 µg/L. However, one study reported effects at 1 µg/L or less. Giesy et al. (2000) reported that exposure to waterborne NP for 42 days at concentrations of >0.3 to 0.4 µg/L appeared to reduce fecundity in fathead minnows, while fish exposed to 0.09 and 0.1 µg/L produced more eggs than control fish, possibly indicating a hormetic response of fecundity to NP. A hormetic response is one that results in a U-shaped dose-response curve, meaning that a response occurs at a low dose, does not occur or occurs to a lesser degree at a higher dose, then reappears or increases at an even greater dose. However, sample sizes used in this study were small, and it is not clear whether the observed effects would be likely to cause population-level impacts in fathead minnows.

K.4 Drinking Water and Wastewater Treatment Technologies

Recently, substantial effort and large amounts of funds have been directed toward assessing the capabilities of WWTP and drinking water treatment plants (DWTP) to remove EDCs and PPCPs. Treatment plant effectiveness at removing these contaminants depends on the properties of the target chemicals and on the treatment process train and operating parameters that are employed. Each wastewater or drinking water treatment process has advantages and disadvantages in terms of effectiveness, cost, and other considerations. For example, reverse osmosis is highly effective at removing most contaminants from drinking water and wastewater (Snyder et al. 2003), but it is costly, and the resulting waste brine presents a serious problem with regard to disposal. Advanced oxidation processes (AOPs) are highly effective at reducing the concentrations of steroids, vary in their effectiveness for other classes of contaminants, and perform poorly for removal of metals and organics (Snyder et al. 2003). Ozonation, chlorination, and AOPs might not actually destroy the target contaminants but rather convert them, at least partially, to byproducts (Petrovic et al. 2003). In many cases, these byproducts or degradation products have not been characterized chemically or toxicologically. In some cases, byproducts appear to retain at least part of the toxicity of the parent compound or might demonstrate even greater toxicity (Hu et al. 2002). Consequently, where oxidation processes are being considered for reduction of toxic effects from wastewater to aquatic organisms, pilot-scale toxicity testing should be conducted prior to installation of costly upgrades and before significant changes to treatment processes are made, to ensure that toxicity is reduced and that treatment byproducts do not cause unexpected toxic effects of their own.

Concentrations of most commonly studied contaminants of emerging concern in wastewater effluent are in the low ng/L range, and often below detection limits (Scruggs et al. 2005), with some notable exceptions. Data presented in Table K-2 show that some of the EDCs and PPCPs analyzed in effluent from a WWTP in the current study area occurred in the higher ng/L range, but all levels were less than 500 ng/L. Although it is understood that effluents from WWTP will contain detectable concentrations of some EDCs and PPCPs, in general, wastewater treatment processes provide a marked reduction in their concentrations. Snyder et al. (2003) reviewed the effectiveness of various water treatment technologies for reducing the levels of different classes of compounds. For comparison, Table K-4 shows the treatment processes used at WWTP in the Las Vegas area.

A variety of treatment technologies are employed at the three WWTP in the study area, and for most classes of EDCs and PPCPS, at least one process rated by Snyder et al. (2003) as "G" (good, 70 – 90 percent) or "E" (excellent, >90 percent) is employed at each plant. For example, each plant uses chlorination, which has an estimated removal efficiency of greater than 90 percent for steroids (a class of EDC). Although chlorination is not very effective (poor <20 percent) to fair (40 – 70 percent) at removing sunscreen agents, each plant uses a degradation step (activated sludge) that is effective in reducing concentrations of these chemicals ("G-E"). Exceptions are the organometallics, lipid regulating drugs, antimicrobials, and surfactants/detergents, which might be removed to a lesser degree than the other classes of EDCs and PPCPs.

Table K-4. Treatment Processes Used at WWTP in the Study Area.

Wastewater Treatment Plant	Activated Sludge	Clarifier	Metal Oxides	Chlorination	Filtration
City of Henderson	X	X	X	X	X
Clark County	X	X	X	X	X
City of Las Vegas	X	X	X	X	X

In general, less is known about EDCs and PPCPs in receiving waters (including source waters for DWTP) and drinking water because analyses for these compounds are rare, and levels often fluctuate around analytical detection limits (Snyder et al. 2003, Scruggs et al. 2005). Many EDCs, such as estrogenic hormones and xenobiotics, appear to be substantially removed during conventional drinking water treatment processes, while these plants generally are not as efficient at removing PPCPs (Snyder et al. 2003).

The drinking water treatment processes used at the three DWTP in the study area are summarized in Table K-5.

As with the WWTP processes, it is possible to compare the treatment technologies used at DWTP in the study area to those with known efficacy at removing certain classes of contaminants. For a review of drinking water treatment process effectiveness for removal of EDCs and PPCPs, see Snyder et al. (2003). It is important to note that that the UV treatment process described in Table 2 of the article by

Table K-5. Treatment Technologies Used at Drinking Water Facilities in the Study Area.

Drinking Water Treatment Plant	Ozone	Coagulation/ Flocculation	UV	Chlorination	Filtration
City of Henderson DWTF		X	X	X	X
Alfred Merritt Smith DWTF	X	X		X	X
River Mountain Water Treatment Facility	X	X		X	X

Snyder et al. (2003) refers to a UV dose much greater than that typically used for disinfection purposes; typical UV doses used for disinfection are relatively ineffective for removal of many contaminants (Shane Snyder, personal communication, April 2006). Information presented here indicates that the DWTPs in the study area that use ozone for disinfection are likely to achieve better removal of some EDCs and PPCPs (industrial chemicals, anti-inflammatory drugs, lipid regulating drugs, and surfactants/detergents, as well as some constituents of other classes) than the plant using UV, assuming that the typical UV dose for disinfection is applied. All of the DWTP should effectively removed steroids (>90 percent), but are expected to perform less efficiently for removal of inorganics.

The concentration of a contaminant remaining in a WWTP effluent or in drinking water depends not only on removal efficiencies of the treatment processes employed, but also on the influent concentration. To determine whether significant benefits are achieved by additional or altered water treatment processes, one would need to characterize influent concentrations, estimate effluent concentrations based on expected removal rates, and compare the estimated effluent concentration to a health-based benchmark. Alternatively, pilot-scale treatment processes can be used to determine effluent or drinking water concentrations, and bioassays can be used to assess changes in toxicity of effluents or drinking water. Bioassays vary in their ability to predict in vivo toxicity to human and ecological receptors, so they should be selected carefully and their results interpreted with caution. Currently, data describing influent concentrations of EDCs and PPCPs in the area WWTP and DWTP are sparse, as are bioassay data for EDCs and PPCPs in area WWTP effluents and drinking water. Furthermore, there currently is no consensus in the scientific community regarding the most appropriate bioassays for EDCs and PPCPs in drinking water or wastewater effluent.

While it might be tempting to set a goal of reducing the concentrations of contaminants of emerging concern in wastewater or particularly in drinking water to levels below the analytical detection limits, this approach is not scientifically valid. First, it is becoming increasingly clear that analytical chemistry techniques are rapidly out-pacing improvements in treatment technologies such that it is impossible to remove all contaminants to levels below detection limits. Furthermore, analytical detection limits may have no relationship to health-based levels of concern. It is possible for toxic effects of a chemical to occur at concentrations less than the achievable analytical detection limits for that chemical. Conversely, as analytical equipment becomes more exquisitely sensitive, it is likely that detectable concentrations for many EDCs and PPCPs will fall far below any concentrations that produce an observable toxic effect. Forcing water treatment technologies to arbitrarily reduce contaminant concentrations below analytical detection limits could result in substantial waste of public funds while achieving no appreciable benefit to public or environmental health. Striving to reach an increasingly unattainable goal of non-detectable levels of contaminants should be abandoned in favor of tailoring drinking water and wastewater treatment goals to achieve concentrations of contaminants of emerging concern that are safe by using the most cost-effective and feasible means.

Because "safe" levels for most EDCs and PPCPs are not known at this time, it is challenging to develop health-based treatment goals. In the absence of regulatory guidelines and toxicity and exposure data required to set health-based goals, each community must determine whether it will wait for additional information and guidance or take proactive measures to treat and remove EDCs and PPCPs from wastewater and drinking water despite the costs and uncertain benefits.

K.5 Conclusions

The toxicological relevance of the occurrence of EDCs and PPCPs in Lake Mead and around the world is under study at this time to determine whether these chemicals are capable of producing adverse effects at environmentally relevant concentrations. There is little evidence to suggest that EDCs and PPCPs in wastewater are having an effect on human populations anywhere. However, substantial evidence from laboratory studies and from field studies in other locations indicates that EDCs and at least one PPCP (EE2) at concentrations that occur in some municipal WWTP effluents can adversely affect fish. While recent research suggests that common carp in the Las Vegas Wash and Las Vegas Bay of Lake Mead might be affected by endocrine disruption, no causative chemical agents or specific sources have been identified. If EDCs or PPCPs are responsible for the reported effects, they might have arisen from WWTP effluent, contaminated groundwater seeps, urban runoff, stormwater flow, or a combination of these. More information would be needed to determine whether the SCOP project is likely to alter potential exposure and effects of EDCs or PPCPs. For example, if contaminants present primarily in the groundwater seeps are responsible for reported effects, removal of the treated municipal WWTP effluent from the Las Vegas Wash might cause these contaminant concentrations to increase in the Las Vegas Wash and inner Las Vegas Bay, though total loading to Lake Mead probably would not change. If contaminants associated primarily with municipal WWTP effluent are causing adverse effects in fish, dilution of the effluent in the main body of the lake might decrease exposure to aquatic organisms in the Las Vegas Wash and inner Las Vegas Bay but increase exposure near the new discharge point, though probably at significantly diluted concentrations. In some cases, passage of treated wastewater through constructed wetlands results in some attenuation of wastewater-related contaminants. However, it is not known whether attenuation of this type currently occurs in the Las Vegas Wash.

K.6 List of Acronyms and Abbreviations

11-KT	11-ketotestosterone
ADI	acceptable daily intake
AOPs	advanced oxidation processes
CAFO	concentrated animal feeding operation
Conc.	concentration
BAF	bioaccumulation factor
BCF	bioconcentration factor
BHC	benzene hexachloride (or hexachlorocyclohexane (HCH))
CCC	criteria continuous concentration
CMC	criteria maximum concentration
DDD	dichlorodiphenyldichloroethane
DDE	dichlorodiphenyldichloroethene
DDT	dichlorodiphenyltrichloroethane
DEET	N,N-diethyltoluamide
DES	diethylstilbestrol
DWTP	drinking water treatment plant
E2	17ß-estradiol
EDSP	Endocrine Disrupter Screening Program
EE2	ethinylestradiol
EAC	endocrine active chemical
EDC	endocrine disrupting chemical
HAA	hormonally-active agent
HHCB	hexahydrohexamethylcyclopentabenzopyran (Galaxolide)
IPCS	International Programme on Chemical Safety
MRL	maximum residue level
NP	nonylphenol
NPE	nonylphenol ethoxylates
OP	octylphenol
OTC	over-the-counter
PAH	polycyclic aromatic hydrocarbon
PCBs	polychlorinated biphenyls
PPCP	pharmaceuticals and personal care products
PhAC	pharmaceutically-active chemical
SPMD	semi-permeable membrane device
TCEP	tris(2-chloroethyl)phosphate
EPA	United States Environmental Protection Agency
FDA	United States Food and Drug Administration
UV	ultraviolet light
VTG	vitellogenin
WWTP	wastewater treatment plant

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