Contaminants of Emerging Concern in the San Francisco Estuary: Carbamazepine

Final Report

Prepared by the Regional Monitoring Program
for Water Quality in the San Francisco Estuary

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SAN FRANCISCO ESTUARY INSTITUTE
4911 Central Avenue, Richmond, CA 94804
p: 510-746-7334 (SFEI), f: 510-746-7300, www.sfei.org

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Rachel Allen, Susan Klosterhaus, and Jay Davis
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I. Use and Production

Carbamazepine (CBZ; Figure 1) is a human pharmaceutical approved by the United States (US) Food and Drug Administration for treating epileptic seizures and trigeminal neuralgia. It is also used "off-label" to treat bipolar depression, excited psychosis, and mania (Thacker 2005). Its suspected mode of action as an anticonvulsant is the reduction of nerve synapse response and blocking of enhanced neural responses following short periods of high-frequency synapse pulses (Snyder et al. 2008). Doses commonly range from 100 to 2000 mg per day.

There is currently no environmental regulation of CBZ. However, since 1999 it has been identified as a reproductive toxin by the State of California (State of California Environmental Protection Agency 2010).

It is estimated that 95,000 and 77,000 pounds of CBZ were produced in the US in 2000 and 2003, respectively (Zhang et al. 2008). Consumption on a per capita basis in the US is lower than in European countries such as Germany, where approximately 192,000 pounds were consumed in 1999. Global consumption is estimated at 2.2 million pounds per year (Zhang et al. 2008).

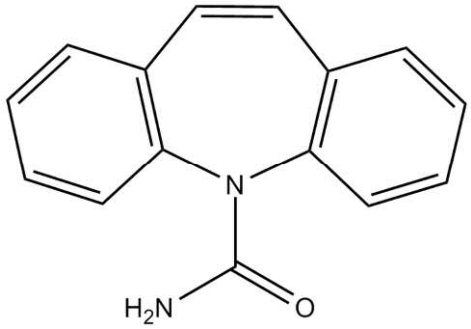

Figure 1. Structure of Carbamazepine (CBZ)

II. Fate in Wastewater Treatment Plants (WWTPs)

From excretion by humans to discharge in WWTP effluent, CBZ is largely conserved in standard wastewater treatment processes. About 30% of the ingested medication is not metabolized in humans and is excreted along with its major metabolites *trans*-10,11-dihydro-10,11-dihydroxycarbamazepine (CBZ-diol) and 10,11-dihydro-10,11-epoxycarbamazepine (CBZ-epoxide). Despite being well-metabolized in humans, CBZ is not degraded in WWTP processes and most removal efficiencies are below 10%. Conventional treatment plants have reported efficiencies that were low (about 10%) and independent of activated sludge retention

time, because CBZ is resistant to microbial biodegradation (Zhang et al. 2008). CBZ is also not removed by membrane bioreactors, which are frequently more effective at removing pharmaceuticals (Sipma et al. 2010). Ozonation (Hua et al. 2006) and UV treatment (Kosjek et al. 2009) have been more effective, removing up to 99% and 93%, respectively, when these treatments were combined with other processes. Potential CBZ degradation products include aza-arenes, which may be toxic and carcinogenic (Kosjek et al. 2009).

Because CBZ has a low affinity for organic matter (K_d = 1.2 L/kg), sorption to sewage sludge is not an effective removal pathway. However, CBZ was detected in the sludge of 96% of 74 WWTPs studied across the US (USEPA 2009). Concentrations ranged from 0.009 to 6 μg/g dry weight (dw), averaging 0.14 μg/g.

Since it is poorly removed during wastewater treatment, CBZ is commonly found in WWTP effluent around the world. Studies in Europe, Asia, and Canada have reported CBZ in effluent at concentrations up to 1.6 μg/L (Heberer et al. 2002), with most ranging from 0.1 to 1 μg/L (Andreozzi et al. 2003, Miao and Metcalfe 2003, Maskaoui and Zhou 2010, Nakada et al. 2010). Effluent concentrations in the US have been comparable, ranging from below detection limits to 1.6 μg/L (Glassmeyer et al. 2005, Snyder et al. 2008, Lubliner et al. 2010). A nationwide survey of WWTPs found a median wastewater effluent concentration of 0.08 μg/L (Glassmeyer et al. 2005). In California, CBZ was detected in effluent from four WWTPs studied in the Southern California Bight region (concentrations not reported) and an unidentified WWTP at 0.19 μg/L (Bay 2008, Guo and Krasner 2009). Though rarely investigated, the metabolites CBZ-diol and CBZ-epoxide were detected in UK effluent from three WWTPs at average concentrations of approximately 1.3 and 0.05 μg/L, respectively (Miao and Metcalfe 2003). Effluent concentrations of CBZ occasionally exceed influent concentrations, which may be due to fluctuations in concentrations that are not accounted for in short term studies, or may be caused by processes in the treatment plant that convert some metabolites back into CBZ (Zhang et al. 2008).

III. Fate and Occurrence in the Environment

Surface Waters

Because it is used solely as a human pharmaceutical, the dominant pathway of CBZ to the aquatic environment is from sewage treatment plants. CBZ is commonly studied because it is one of the most frequently detected pharmaceuticals in water bodies and it has been proposed as a marker of human waste (Clara et al. 2004).

CBZ is one of the most persistent pharmaceuticals in estuarine environments. In the environment, as in wastewater treatment plants, CBZ is resistant to microbial degradation, has low adsorption to sediment, and undergoes limited photodegradation (Andreozzi et al. 2003, Clara et al. 2004). The main removal processes in aquatic environments are therefore flushing and dilution. The half-life of CBZ in aquatic ecosystems is reported to range from 63 to 328 days (Loffler et al. 2005). In a laboratory study comparing the degradation of 19 pharmaceuticals in coastal waters, Benotti and Brownawell (2009) determined that CBZ was one of the most persistent pharmaceuticals, with a half-life of over 100 days. Chiron et al (2006) reported that the

photodegradation rate of CBZ was three times faster in estuarine conditions relative to freshwater, and that one major intermediate of CBZ photodegradation is the toxic compound acridine. The human metabolite CBZ-diol has an environmental half-life of eight days, and it appears to have less capacity for sorption to sediment compared to CBZ due to its high water solubility (Loffler et al. 2005).

CBZ is widespread in water bodies throughout the world, with concentrations generally decreasing with distance from potential sources such as wastewater effluent discharge (Zhang et al. 2008, Cunningham et al. 2010). The highest concentration reported (11 μg/L) was detected in a survey of over 100 streams in the European Union (Loos et al. 2009). In this study, CBZ was detected in 95% of streams surveyed, at a median concentration of 0.075 μg/L. Tixier et al (2003) reported concentrations up to about 0.35 μg/L in rivers entering Lake Greifensee, Switzerland, and up to 0.04 μg/L in the surface waters of the lake. In the US, CBZ was detected at a maximum concentration of 1.5 μg/L in a stream highly impacted by municipal wastewater (Stackelberg et al. 2004). Two nationwide surveys in the US detected CBZ in a majority of rivers sampled. In ten streams receiving WWTP effluent discharges, CBZ was detected at low levels (below 0.01 μg/L on average) upstream of effluent discharges, but at a median concentration of 0.08 μg/L downstream (Glassmeyer et al. 2005). The second nationwide study detected an average concentration of 0.06 μg/L among 44 rivers (Thacker 2005). In a California stream highly impacted by wastewater, CBZ was recently detected at 0.13 μg/L (Guo and Krasner 2009). Seawater concentrations are generally much lower than river concentrations, although CBZ has been detected at 0.32 μg/L at a wastewater-impacted site in the Scheldt Estuary, Belgium (Wille et al. 2010). Concentrations off the North Sea coast ranged from below detection to 0.019 μg/L, while urban harbor sites had average concentrations that ranged from 0.015 to 0.2 μg/L (Wille et al. 2010). In an older study, CBZ was detected at a concentration of about 0.002 μg/L in the German Bight (Weigel et al. 2001). In the US, CBZ was detected but not quantified in one out of four samples from the Southern California Bight (Bay 2008). In general, these studies have targeted surface waters expected to be highly impacted by wastewater effluent, so they should not be considered necessarily representative of surface water conditions.

Surface Sediment

CBZ is relatively hydrophilic, and consequently, few studies have reported sediment concentrations. In rivers in Germany, sediment concentrations ranged from 4 to 50 ng/g dw (Stein et al. 2008). Maskaoui and Zhou (2010) reported CBZ concentrations of 1 to 140 ng/g dw in suspended particulate matter in a UK river. In a survey of 44 US rivers, the average CBZ sediment concentration was 4 ng/g dw (Thacker 2005).

Wildlife

Few studies have investigated the presence of CBZ in wildlife and none have reported concentrations of CBZ in algae or invertebrates in aquatic environments. CBZ has been detected in fish from effluent-influenced streams in two studies. In Texas, CBZ concentrations in freshwater sunfish ranged from 0.8 to 1.4 ng/g wet weight (ww) (mean 1.2 ng/g ww), and it was not detected in fish from the pristine stream also sampled in the study (Ramirez et al. 2007). In a nationwide pilot study of fish in US streams, CBZ was detected in fish at only one of five

wastewater-impacted sites (Ramirez et al. 2009). In that study, mean concentrations in largemouth bass from the Chicago site were 6 ng/g ww in liver tissue and 2 ng/g ww in the fillets. In California coastal waters, Kwon et al (2009) analyzed CBZ in turbot; however, it was not detected in any of the ten samples analyzed (detection limit 4 ng/g ww).

IV. Toxicity

Because CBZ is commonly detected in aquatic environments, understanding its effects on aquatic organisms is essential for assessing its potential impact. However, the reported ecotoxicity of CBZ varies widely and its mode of action in aquatic organisms is not well studied. In humans, CBZ functions as an anti-convulsant by suppressing overall neuronal activity in the central nervous system, and some of its potency derives from its interference with cell communication (Fent et al. 2006, Martin-Diaz et al. 2009). This neurochemical pathway may be shared among many different organisms. Martin-Diaz et al. (2009) showed that exposure to CBZ also reduced neurotransmitter levels in Mediterranean mussels, suggesting that CBZ may also impact neurochemical pathways in aquatic organisms.

Most studies investigating acute and chronic effects of CBZ on aquatic organisms have used traditional standardized toxicity tests, and have observed effects at water concentrations above 25 µg/L (Table 1). Using the traditional tests, CBZ is generally most toxic to invertebrates, followed by fish and algae. CBZ has been predicted to have no adverse effects on aquatic organisms at concentrations below 0.4 µg/L (Ferrari et al. 2003) and 6.4 µg/L (Jos et al. 2003). An exception to this is the lowest observed effects concentration (LOEC) of 0.1 µg/L, which induced oxidative stress and reduced lysosomal membrane stability, an index of general health status, in the marine mussel *Mytilus galloprovincialis* (Martin-Diaz et al. 2009). Although CBZ has been primarily detected in the dissolved phase, a no observed effects concentration (NOEC) of 140 ng/g dw in sediment was determined for CBZ in a laboratory study using the freshwater invertebrate *Chironomus riparius* (Oetken et al. 2005). In addition, it has been suggested that CBZ could have synergistic effects with other chemicals (Cleuvers 2003, Jos et al. 2003, Dietrich et al. 2010). Water quality guidelines for CBZ have not been developed; however, CBZ is labeled as "harmful" in accordance with European Commission directives (Quinn et al. 2008).

Table 1. CBZ toxicity threshold values for aquatic organisms using traditional methodologies

Indicator Organism	Acute Effects Thresholds (µg/L)	Chronic Effects Thresholds (µg/L)
Algae	20,000[1] - 36,600[b]	25,500[c] - >100,000[d]
Invertebrates	9900[e] - >100,000[f]	25[d] - 77,700[g]

[1] Andreozzi et al. 2002; [b] Jos et al. 2003; [c] Cleuvers 2003; [d] Ferrari et al. 2003; [e] Dussault et al. 2008; [f] Kim et al. 2009; [g] Ferrari et al. 2004

V. Potential Impacts in San Francisco Bay

Bay Data

In January 2010, whole water, sediment, and resident mussel samples were collected from five nearshore sites (Central, South, and Lower South Bays) and analyzed for CBZ as part of a pilot study investigating contaminants of emerging concern in the Bay (Table 2).

- CBZ was detected in surface water at all five sites (mean 0.018 ± 0.016 µg/L). These concentrations are comparable to the few studies that have investigated CBZ in coastal waters.
- CBZ was not detected in sediment at any of the sites (detection limit 4.4 ng/g dw).
- CBZ was detected in mussel tissue at all five sites (mean 3 ± 1.7 ng/g ww).

Concentrations in water were generally correlated with tissue concentrations, with the highest concentrations of CBZ detected in the South Bay. Higher concentrations in the South Bay likely result from the discharge of municipal wastewater into surface waters that experience less dilution and have higher residence times compared to other Bay segments. In 2009, it was estimated that 0.12 kg of CBZ per day was discharged from a South Bay wastewater treatment plant (Dunlavey et al. 2009).

Table 2. Carbamazepine in San Francisco Bay Water, Sediment, and Mussels

Sample Site	Water (µg/L)	Sediment (ng/g dry weight)	Mussel Tissue (ng/g wet weight)
Richmond (Central Bay)	0.0052	<4.4	1.6
San Leandro Bay (Central Bay)	0.0078	<4.4	1.3
Eden Landing (South Bay)	0.016	<4.4	5.3
Cooley Landing (South Bay)	0.044	<4.4	4
Foster City (South Bay)	0.015	<4.4	2.4
San Francisco Bay margins (average)	**0.018**	**<4.4**	**3**

Potential Impact

Concentrations of CBZ in San Francisco Bay water (maximum 0.044 µg/L) were generally well below concentrations expected to elicit toxic effects in aquatic organisms (≥ 25 µg/L). However, because CBZ accumulated in Bay mussels and recent results have suggested that it could induce oxidative stress and reduced lysosomal membrane stability in mussels exposed to water concentrations as low as 0.1 µg/L (Martin-Diaz et al. 2009), there is a potential for effects on Bay mussels due to CBZ exposure.

While CBZ was detected in San Francisco Bay surface waters at concentrations below toxicity thresholds, it may be present at higher concentrations closer to wastewater outfalls, thus increasing the possibility of toxic effects. Organisms living near WWTP outfalls would also be

exposed to other pharmaceuticals and toxic substances that have been identified in WWTP effluent, which may result in additive effects. Few studies have investigated the potential for sub-lethal impacts on populations due to long-term exposures to low concentrations of CBZ; these studies would be needed for a thorough assessment of its risk to aquatic life in the Bay.

For humans, numerous risk assessment studies have predicted that there is no potential for adverse effects due to ingestion of CBZ in fish or drinking water (Snyder et al. 2008, Cunningham et al. 2010, Kumar and Xagoraraki 2010).

VI. Key Information Gaps

- More information is needed on the potential effects on Bay aquatic life due to long-term exposure to concentrations of CBZ .

- More information is needed on the concentrations of CBZ in surface waters and biota near Bay Area treatment plant outfalls, where exposures are anticipated to be highest.

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