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Biological effects of anthropogenic contaminants in the San Francisco Estuary

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Abstract

Concentrations of many anthropogenic contaminants in the San Francisco Estuary exist at levels that have been associated with biological effects elsewhere, so there is a potential for them to cause biological effects in the Estuary. The purpose of this paper is to summarize information about biological effects on the Estuary's plankton, benthos, fish, birds, and mammals, gathered since the early 1990s, focusing on key accomplishments. These studies have been conducted at all levels of biological organization (sub-cellular through communities), but have included only a small fraction of the organisms and contaminants of concern in the region. The studies summarized provide a body of evidence that some contaminants are causing biological impacts in some biological resources in the Estuary. However, no general patterns of effects were apparent in space and time, and no single contaminant was consistently related to effects among the biota considered. These conclusions reflect the difficulty in demonstrating biological effects due specifically to contamination because there is a wide range of sensitivity to contaminants among the Estuary's many organisms. Additionally, the spatial and temporal distribution of contamination in the Estuary is highly variable, and levels of contamination covary with other environmental factors, such as freshwater inflow or sediment-type. Federal and State regulatory agencies desire to develop biological criteria to protect the Estuary's biological resources. Future studies of biological effects in San Francisco Estuary should focus on the development of meaningful indicators of biological effects, and on key organism and contaminants of concern in long-term, multifaceted studies that include laboratory and field experiments to determine cause and effect to adequately inform management and regulatory decisions.

Keywords: Biological effects; Contamination; San Francisco Estuary

1. Introduction

The San Francisco Estuary (hereafter called the Estuary, Fig. 1) receives large volumes of freshwater inflow that transport agricultural, stormwater, and wastewater discharges into the Estuary (Davis et al., 2000). Many of the associated anthropogenic contaminants, as well as several naturally occurring trace elements (nickel (Ni), selenium (Se), chromium (Cr)) are present in water and sediment in concentrations that exceed water quality objectives, or sediment quality guidelines (e.g., Long et al., 1995). Many contaminants, as well as contaminant mixtures, have the potential to cause toxic effects on estuarine organisms.

The objective of this paper is to synthesize and summarize information about biological effects in the Estuary. The information presented in this paper includes

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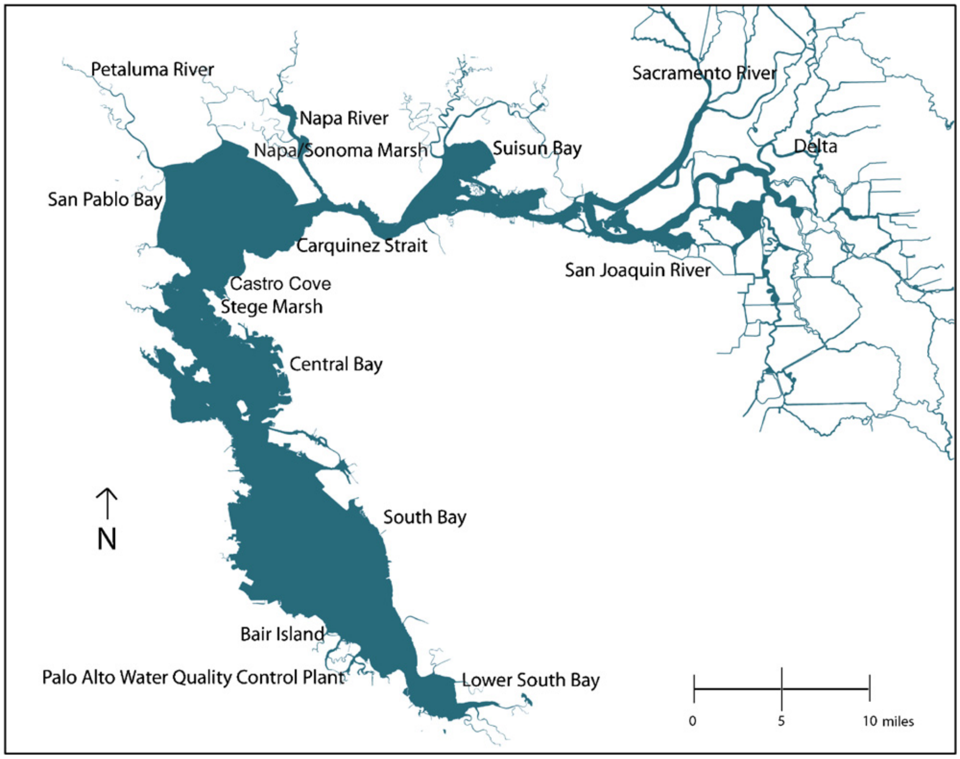

Fig. 1. Map of the San Francisco Estuary and Delta showing locations referenced in this paper.

studies conducted in the region by federal or local agencies, universities, non-governmental, and private organizations. Summaries of contaminant effects in the Estuary were produced in the early 1990s: The San Francisco Estuary Project (US EPA National Estuary Program) produced Status and Trends reports on pollutants (Davis et al., 1991) and on aquatic life (Herbold et al., 1992) that included summaries of knowledge about biological effects of contaminants in the Estuary at that time. This paper focuses on studies of toxic effects of contaminants to estuarine animals conducted since those reviews were completed.

Although bioaccumulation is an integral and extremely important aspect of toxicity, in this paper we present information on accumulation of contaminants only where it has been linked to effects. Other papers in this volume provide information on bioaccumulation of specific contaminants. A synthesis of sediment toxicity studies is included in another paper in this volume (Anderson et al., 2006), and a summary of aquatic toxicity studies is included in Ogle et al. (2001).

The enduring challenge in effects studies is isolating biological variability due to contaminant effects from those effects due to other factors such as salinity, substrate, food, and various ecological processes (Luoma, 1996; Thompson et al., 2000; Cloern and Dufford, 2005). Probably the most important of these processes in the San Francisco Estuary is the annual and seasonal variability in freshwater inflows from the Delta that expose organisms to changes in salinity, river-borne contaminant inputs, carbon load, and the distribution of sediments and contaminants. Understanding the patterns in both year-to-year and seasonal variability of river inflow and freshwater diversion is critical to understanding the differences between natural and anthropogenic effects on the ecosystem.

1.1. Background

One of the main objectives of federal statutes such as the Clean Water Act (CWA), Endangered Species Act (ESA), Migratory Bird Treaty Act (MBTA), Marine Mammal Protection Act (MMPA), and essential fish habitat (EFH) provisions of the Magnuson–Stevens Fishery Conservation and Management Act, as well as the California Porter-Cologne Water Quality Control Act (Porter-Cologne), is to protect biological resources. The CWA and Porter-Cologne focus primarily on the impact of chemical and physical water quality conditions on populations and communities, while the other statutes have considered a broader range of potential impacts on the health of individual animals. The CWA and Porter-Cologne provide the basis for California Regional Water Quality Control Plans (Basin Plans), which include lists of ''Beneficial Uses'' that include protection for aquatic life, wildlife, and rare and endangered species. However, definitions of acceptable biological condition are not included in those regulations, probably due to incomplete scientific knowledge in most habitat types, and the lack of agreement on what constitutes a healthy population or community under various environmental conditions, for policy purposes (e.g., Regan et al., 2002).

The San Francisco Bay Regional Water Quality Control Board (Water Board) is responsible for the protection of beneficial uses in the Estuary. Since California does not currently have regulatory biological criteria, the main regulatory mechanisms used for such protection include numerical water quality objectives for the concentrations of contaminants in estuarine waters and narrative objectives, which state: "All waters shall be maintained free of toxic substances in concentrations that are lethal to or that produce other detrimental responses in aquatic organisms. Effects on aquatic organisms, wildlife, and human health will be considered." The difficulty in identifying biological effects specifically related to contamination is recognized by the Water Board. However, it is necessary to identify the specific contaminant(s) that cause adverse effects so that cost-effective, efficient remedies, and management strategies can be developed. Historically, the Water Board has used laboratory toxicity tests as the primary indicator of biological effects from contaminants. Benthic community analyses were also used as a component of the Bay Protection and Toxic Clean-up Program in the 1990s (Hunt et al., 2001). The Water Board instituted the San Francisco Estuary Regional Monitoring Program (RMP) in 1993. The RMP has included only a few measurements of biological effects, such as water and sediment toxicity tests, benthic macrofauna, and bivalve and fish condition measurements.

1.2. Mechanisms and models of biological effects

Aquatic organisms may be exposed to contaminants contained in water, sediments, and food (Landrum and Robbins, 1990; Forbes et al., 1998; Weston and Mayer, 1998). The amount of contaminant assimilated depends on its chemistry (electrical charge, polarity, size, and steric factors), and the organisms' biology. Contaminants may enter by absorption through the respiratory surfaces, skin or digestive tract. Once contaminants enter the organism, they can be distributed to various organs or fluids depending on their chemical form, the characteristics of the organ (lipid content or binding capacity) or fluid. The flux of the contaminant in the organism (rate of accumulation, transformation, and loss) determines the tissue concentrations. Portions of ingested contaminants may pass through the organism and be excreted. Metabolism and excretion may reduce tissue contaminant concentrations (e.g., Waalkes and Perez-Olle, 2000; Ramalingam, 2003).

Contaminant effects on an organism may occur by direct effects through chemical toxicity, or by indirect toxic effects that may change the prey or competitors of an organism, affecting food supply or habitat availability (Fleeger et al., 2003). Direct effects usually occur when the biochemistry and physiology of an organism are altered by abnormal chemical action, or when the compensatory and repair processes elicited in the organism by toxic chemicals consume energy that detracts from growth, reproduction, or general fitness. Several mechanisms of chemical toxicity are recognized (Klaassen, 2001; Landis and Yu, 2004). They include interruption, blocking, or interference of specific cellular functions, such as the increased production of highly reactive molecules (e.g., H_2O_2), macrophage disruption (e.g., Weeks et al., 1990), enzyme induction (e.g., P450; Spies et al., 1993), interference at nerve synapses (neurotoxicity, e.g., Buznikov et al., 2001), hormone receptors (e.g., endocrine disruptors, Roepke et al., 2005), or immunoreceptors (e.g., Luengen et al., 2004). Nucleic acids may be broken or bound to reactive molecules (genotoxicity, e.g., Neale et al., 2005b). Cellular responses to exposure to contamination may include stimulation of protection mechanisms, such as lysosomes (Lowe et al., 1995) and stress proteins (Werner and Nagel, 1997). Tissue (histological) damage may occur as a result of these cellular processes (e.g., Mitra, 2003), and may result in developmental abnormalities (teratogenic effects; e.g., Heinz, 1996). Measures of certain cellular and tissue effects are often used as biomarkers to provide evidence of exposure to contamination and as indicators of effects. Biomarkers, such as stress proteins and macrophage disruption do not reflect exposure to specific contaminants. Others, such as P450 induction and metallothionein concentrations, may indicate exposure to certain classes of contaminants, or reflect specific toxicity pathways. Histological changes and DNA damage may indicate both exposure and effects.

At the organism level, dose-response kinetics have been established for relatively few organisms and toxic endpoints, and for only the most common contaminants (Landis and Yu, 2004). Increases in contaminant concentrations usually produce a curvilinear effect response; the inflection is generally considered to be an effect threshold. At very high doses, mortality occurs within hours or days (acute effects). However, environmental concentrations are usually below acute levels, and effects may be observed as decreased growth rates, reduced life span, reproductive impairment, or teratogenic effects in offspring (chronic effects). More subtle effects on individual organisms may be measured using biomarkers or observed as behavioral changes. Effects on individual organisms, such as changes in growth, reproduction, or mortality, may result in changes in local populations (MacArthur and Connell, 1966; Kuhn et al., 2002), and changes in populations may affect species composition, which shapes communities and ecosystems. These population and community changes are very difficult to relate specifically to contamination because the changes may also be affected by numerous environmental and ecological factors.

Models for the response of benthic organisms to pollutants and organic material were described by Pearson and Rosenberg (1978), and recently expanded to sediment contamination by Thompson and Lowe (2004). These models include consideration of toxicological and ecological processes. Loss of sensitive taxa and persistence of tolerant taxa results in community measures, such as taxa richness and biomass, which exhibit non-linear responses to contamination. The highest community values occur at intermediate or moderate organic material and/or contamination levels. At the highest contaminant concentrations, acute toxicity eliminates most benthic organisms in the affected area.

2. Results

2.1. Plankton

Plankton dynamics in San Francisco Bay are the subject of ongoing and extensive studies (Jassby and Powell, 1994; Cloern, 1996; USGS, 2005). About 500 taxa are present in phytoplankton communities of San Francisco Bay. Diatoms represent about 81% of the biomass (Cloern and Dufford, 2005), and bacterioplankton biomass contributes about 16% of phytoplankton biomass (Hollibaugh and Wong, 1996). Plankton are generally considered to be at the base of the estuarine energy and food webs with key functions of transforming the chemical and physical forms of contaminants and contaminant transport to higher trophic levels. There have been very few studies of biological effects of contamination on plankton in the Estuary. Most contaminant-related studies of plankton have focused on contaminant-specific uptake and loss processes for individual species. In other estuaries as well as San Francisco Bay, contaminant distribution data and laboratory bioassay results have been synthesized to speculate on the environmental risk of certain contaminants to planktonic species (Werner et al., 2000; Pennington et al., 2001). But as with other major estuaries, researchers studying planktonic communities in San Francisco Bay are challenged to quantitatively demonstrate a connection between documented contaminants loads and ecosystem response.

The highest bioaccumulation factors between trophic levels for contaminant solutes typically occur at the planktonic base (Fisher and Reinfelder, 1995). Modes of cadmium (Cd), Ni, and zinc uptake by phytoplankton in the Estuary have demonstrated that biologically driven contaminant solute flux can cause, at least episodically, major repartitioning that significantly decreases water-column concentrations. Metal–organic complexes in plankton tissue may be exploited by predators. The clams *Corbula* (formerly *Potamocorbula*) *amurensis* and *Macoma balthica* assimilated Cd and zinc more efficiently from microalgal particles than from inorganic suspended sediments. It was hypothesized that the trace metal enriched cystolic fractions of the microalgal cells enhanced absorption efficiency of these metals by the clams (Luoma et al., 1998; Lee and Luoma, 1998). Cd and silver (Ag) accumulation by the estuarine amphipod *Leptocheirus plumulosus* was also observed by Schlekat et al. (2000a). In laboratory experiments, Ag uptake by zooplankton appeared dependent on the cytoplasmic distribution of Ag in phytoplankton prey and on digestive pathways (Fisher and Wang, 1998; Xu and Wang, 2004).

Purkerson et al. (2003) observed Se concentrations in zooplankton in the range of 1.02–6.07 $\mu g\,g^{-1}$ dry weight, similar to the range of 1.5–5.4 $\mu g\,g^{-1}$ estimated by Schlekat et al. (2004) in modeling studies, but lower than the observed range for bivalves (4.5–24 $\mu g\,g^{-1}$). Schlekat et al. (2002) observed significant differences in the relative cytoplasmic concentrations of Se between five phytoplankton species that were, in turn, assimilated more efficiently by *C. amurensis* than *L. plumulosus*. The authors also observed major differences in assimilation efficiencies between phytoplankton-consuming bivalves and noted that "changes in the composition of the phytoplankton community… could affect Se accumulation in the bivalve *Macoma balthica* but less so for *C. amurensis*." Consistent with these studies, Stewart et al. (2004) demonstrated how a pelagic, crustacean-based food web generated a lower trajectory for Se trophic transfer than a benthic, clam-based food web.

Microcosm experiments by Beck et al. (2002) demonstrated constrained rates of copper (Cu) or Ni uptake by major diatom species in the Estuary due to the low bioavailability of metals that were predominantly organically chelated (i.e., cupric-ion activity of the order of 10^{-12} M). Although not true for all contaminants, the bioavailability of the free (uncomplexed) Cu or Ni ion suggests that the chemical forms of a contaminant, which can be determined by chemical-speciation programs or various trace-analytical techniques, often reduce to one or two dominant forms. Beck et al. (2002) also observed that elevated Cu concentrations affected manganese removal from solution, supporting the toxicological mechanism of Cu interfering with manganese assimilation. This suggests a co-dependence between the phytoplankton uptake rates for trace constituents like Cu and manganese. However, these studies also suggested minimal toxicological effect on the phytoplankton community by Cu and Ni. Field and laboratory studies by Donat et al. (1994) and by Kuwabara et al. (1996) indicated the management importance of trace-metal speciation in the South Bay due to metal complexation with high-affinity ligands that reduce bioavailability.

Uptake and assimilation rates for contaminants have dual ecological significance because they represent the potential for impairment through succeeding trophic levels, and for biologically induced changes in contaminant distributions in this urbanized Estuary (Luoma et al., 1998). For mercury (Hg), uptake rates on the order of 10^{-15} mole Hg cell^{-1} h^{-1} (moles of Hg per cell per hour) for uncharged methylmercury (CH_3HgCl or CH_3HgOH) and inorganic mercury ($HgCl_2$) are of particular interest with methylmercury accumulating about four times more efficiently by diatoms than the uncharged chlorocomplex (Mason et al., 1996). These authors found that growth by the marine diatom *Thallasiosira weissflogii* was inhibited at dissolved methylmercury concentrations greater than 80 pM. Although dissolved concentrations in the water column of the Estuary are consistently below 3 pM (Conaway et al., 2003; Topping et al., 2004), elevated Hg concentrations in upper-trophic level organisms (see subsequent sections) indicate that trophic-transfer of Hg is significant to human health in the Estuary and in surrounding watersheds (Kuwabara et al., 2005).

For Se, uptake rates vary considerably within and among phytoplankton groups (10^{-21}–10^{-18} mole cell^{-1} h^{-1}); organic selenides and inorganic selenite are chemical forms of greatest significance (Baines and Fisher, 2001; Baines et al., 2001). Ag uptake rates for phytoplankton (10^{-18}–10^{-16} mole cell^{-1} h^{-1}) depend on nutrient concentrations where the uncomplexed Ag^+ ion and the uncharged chlorocomplex ($AgCl^0$) are potentially most bioavailable (Fisher and Wang, 1998; Xu and Wang, 2004).

Since Gavis et al. (1981) and Brand and Sunda (1986) described the relative toxicity of cupric-ion activity to various phytoplankton species or groups, few comparable studies have been reported for other contaminants. Contaminant effects on the phytoplankton are related to temporally and spatially variable contaminant speciation and partitioning. Contaminant effects based on assumptions about the consistency of phytoplankton community structure are questionable given the variability of solute uptake by various phytoplankton species (e.g., for selenite, Baines and Fisher, 2001). These assumptions could be tested by examining the interannual variability in the shift of dissolved-solute concentrations associated with spring phytoplankton bloom biomass as suggested by Luoma et al. (1998).

There is virtually an information void on the subject of trace organic contaminant effects on phytoplankton in the Estuary. No significant herbicide effects on phytoplankton primary production in the Delta (May–November) were observed by Edmunds et al. (1999). They noted that diuron, atrazine, cyanazine, simazine, thiobencarb, and hexazinone concentrations were consistently below those where significant toxicological effects had been observed in laboratory experiments by others. In a synthesis of pesticide data for surface waters in the United States, however, Larson et al. (1999) noted elevated concentrations of the orchard herbicide simazine (0.05–$>$0.5 nM, MW 201.7 Da) and four insecticides (chlorpyrifos, diazinon, carbofuran, and carbaryl) at three sites within the San Joaquin Basin relative to 37 other agricultural indicator sites.

Field studies of contaminant effects on zooplankton in San Francisco Estuary are rare, particularly for inorganic contaminants (Purkerson et al., 2003). However, laboratory toxicity tests have shown the potential for impacts on mysids and daphnids due to herbicides and insecticides in the Estuary and Delta (Foe, 1995; Kuivila and Foe, 1995, De Vlaming, 1996; Ogle et al., 2001). Aquatic bioassay results spanning 1997–2000 suggested a link between episodic pesticide runoff into the Estuary and aquatic toxicity to mysid shrimp, a non-resident test organism (Ogle et al., 2001). Furthermore, within the back sloughs of the Sacramento-San Joaquin River Delta, Werner et al. (2000) observed the greatest percentage (14.1–19.6% between 1993 and 1995) of samples toxic to *Ceriodaphnia dubia* caused by organophosphate and carbamate pesticides. In addition to herbicides and insecticides, Kolpin et al. (2002) and Smital et al. (2004) shed light on the pervasive presence of synthetic, hormonally active, organic chemicals in our nation's surface waters. Roepke et al. (2005) demonstrated that the toxicity of such endocrine disrupting compounds on echinoderm embryonic development, particularly in the blastula stage, could be expressed at concentrations as low as 0.2 nM (MW 140–250 Da). Although, the toxicological mechanism was not identified, more than one mode was suggested.

In summary, models that quantify the primary effects of inorganic and organic contaminants on planktonic species, let alone multi-solute interdependent effects on planktonic communities, are critically limited considering that these toxicological effects can extend cumulatively to the higher trophic levels discussed below. Beyond the limitations summarized in this section, a clear void lies in our knowledge of picoplankton communities. Despite the fact that picoplankton (both autotrophic and heterotrophic) represent significant biological surface area for contaminant exchange in the Estuary's water column (Hollibaugh and Wong, 1996; Ning et al., 2000), there is a conspicuous absence of contaminant studies on this planktonic group.

2.2. Benthic invertebrates

Benthic organisms inhabit the intertidal and subtidal sediments of the Estuary. Indicators of benthic condition are used in assessments of environmental condition in most coastal monitoring programs in the US (US EPA, 2005) because they are an important ecosystem component with generally limited motility, they link sediment contamination to the food web, and their burrowing activity affects sediment stability and geochemistry. Two approaches have been taken in San Francisco Estuary benthic studies: biological effects of trace metal contamination on selected species or sub-populations, and community or population effects that correlate with varying levels of sediment contaminant mixtures.

Ag is highly toxic and readily accumulated as a result of its reactivity with chlorides in seawater and its binding capacity with suspended sediment particles (Luoma et al., 1995). Elevated concentrations of Ag are almost always of anthropogenic origin. Following decreased loadings in wastewater effluent, Ag concentrations in the clam *Macoma balthica* and in sediment collected near the Palo Alto Water Quality Control Plant declined by 87% between 1977 and 1991. Prior to 1989 when the concentrations of Ag were elevated, mature gonadal tissues were not observed in more than 50% of the clams. After contamination decreased in 1989, *Macoma balthica* again developed mature gonadal tissues, and the reproductive capabilities of clams improved (Hornberger et al., 2000). Ag effects on the clam *Corbula amurensis* (formerly *Potamocorbula*) were studied at a number of sites from San Pablo Bay to Suisun Bay from 1990 to 2000. Ag in the clams showed a negative relationship with condition index, and was also correlated with changes in reproductive activity (Parchaso and Thompson, 2002). When Ag concentrations in the tissues were highest, clams were reproductively active only 20–60% of the year. However, when Ag concentrations in the clams were below 1 $\mu g\, g^{-1}$ dry weight, the clams were reproductively active 80–100% of the year. These observations suggest chemical disruption of reproduction by Ag. Other environmental factors show no such association and are unlikely causes (Brown et al., 2003).

Several studies have focused on Se uptake and effects in the dominant estuarine clam *C. amurensis*. Se is a necessary micronutrient, but at slightly higher concentrations, is a reproductive toxin. Se has not been linked to toxicity in Estuary clams, but is bioaccumulated through the food web. Se accumulation at the highest trophic levels in the Bay was five-fold greater through the clam-based food web than through the crustacean-based food web (Stewart et al., 2004; Linville et al., 2002). Clams have a 10-fold slower rate constant of loss for Se than do copepods and mysids, resulting in much higher Se concentrations in the bivalves than in the crustaceans (Schlekat et al., 2000b, 2002). High concentrations of Se in *C. amurensis* often exceed values known to reduce growth or cause reproductive damage when ingested by birds and fish (Lemly, 1998; Hamilton, 1999; Heinz, 1996).

Cd is a non-essential element and competes with zinc for binding sites, which interferes with the essential functions of zinc by inhibition of enzyme reactions and utilization of nutrients. The bioavailability of Cd to *C. amurensis* appears to be driven by salinity. Cd is more available to fresh water biota because it exists principally in the free-ion form, which is highly available. In more saline waters, Cd forms chloro-complexes, which make it less available. The spatial gradient of Cd in clam tissues is correlated to the salinity gradient, consistent with this change in chemical form (Brown et al., 2004). Cd may affect the clam, but the mechanism is not clear. Condition index measurements in *C. amurensis* showed a significant negative correlation with Cd tissue concentrations. Clams with high Cd concentrations did not gain or lose weight in seasonal cycles as did clams with low Cd concentrations. Changes in condition index could also be driven by changes in reproduction, growth, or energy reserves (glycogen and lipids), but these factors have not been studied fully.

The effects of Cu on bivalves were studied by following changes in Cu loadings from the Palo Alto Water Quality Control Plant. As Cu decreased in the surface sediment as a result of improved source control and treatment, Cu also decreased in the tissues of the bivalve *Macoma balthica* (Hornberger et al., 2000), similar to their Ag results. The reproductive capability of the clams improved in association with the decrease in tissue concentrations. The San Francisco Estuary RMP has consistently showed that sediment from Grizzly Bay was toxic to bivalve larvae (*Mytilus galloprovincialis*). Through a combination of methods, Phillips et al. (2003) showed that Cu was the most probable cause of this toxicity.

The disruption of processes associated with key population response factors, such as reproduction, has been linked to increased trace metal body burdens using enzymatic and histopathological biomarkers as indicators of exposure and effects (Teh et al., 1999). Histopathologic analysis of digestive glands, kidney tubules, gill, and gonadal tissue revealed no lesions in *C. amurensis* with the lowest overall metal concentrations (San Pablo Bay). As metal concentrations increased in the clams at the different sites, the number of lesions increased. Severe lesions in all tissues examined were found only in clams with the highest metal concentrations (eastern Suisun Bay), and enzymatic analysis revealed increased digestive diverticula ATP. It was postulated that changes in population dynamics were related to increases in metal body burdens, increases in ovarian and testicular necrosis, decreases in condition index and glycogen content, and decreases in reproductive output (Teh et al., 1999). Immune responses to contamination in the mussels *Mytilis californianus* and *Mytilis galloprovincialis/troussulus* were observed at two South Bay sites, where the mussels had elevated levels of phagocytosis (Luengen et al., 2004).

Cr, Ni and vanadium (V) are mostly of geological origin, but they are potentially toxic contaminants. Specific forms of Cr, Ni, and V that commonly occur in aquatic environments are known to be toxic, but little is known about their bioavailability in estuaries. The seasonal pattern of Cr, Ni, and V concentrations in the tissues of *C. amurensis* indicates that freshwater flow into the Bay from the Delta affects their bioaccumulation. These metals do not appear to have a direct effect on benthic organisms, but their accumulation in bivalves contributes to an understanding of the processes that determine the fate of these contaminants (Brown et al., 2004).

Two important classes of contaminants that are not well studied in the context of benthic invertebrates in San Francisca Bay, but are of great concern, are polycyclic aromatic hydrocarbons (PAHs) and pyrethroid pesticides. PAHs originate from many sources including motor vehicles and petroleum spills, and may accumulate in estuarine sediments. The only studies of PAH effects on invertebrates in the Estuary associated amphipod toxicity with seasonal changes in sediment PAH concentrations at two Central Bay sites (Thompson et al., 1999). Studies on the effects of PAHs to invertebrates have been conducted elsewhere and have shown impacts on immune systems and DNA damage, (Clément et al., 2005; Wootton et al., 2003).

Pyrethroids are the active ingredients in most insecticides available for residential use in the United States. Pyrethroids in most sediments of urban creeks in the Central Valley caused toxicity in laboratory exposures to the amphipod *Hyalella azteca* and about half the samples caused nearly complete mortality (Weston et al., 2005). Ultralow doses of pyrethroids have showed toxic effects on *Daphnia magna* (Ratushnyak et al., 2005).

Benthic assemblage (community) impacts associated with contaminated sediments have been observed in several locations in the Estuary. Assessments of benthic condition using a multimetric Index of Biotic Integrity (IBI) were conducted on samples from two major benthic assemblages in the Estuary: the polyhaline assemblage in the Central Bay and the mesohaline assemblage from the moderate salinity portions of the Estuary (Thompson and Lowe, 2004). Several degrees of impacts were defined based on the cumulative number of exceedances of reference sample ranges (multiple sites in each assemblage) for selected benthic indicators in each sample assessed. Only 2.5% of the samples from the deeper, offshore benthic habitat showed apparent impacts; 14.3% of the samples from near wastewater discharges showed impacts, and 78.3% of the samples from sub-embayments and channels around the Estuary margin were impacted. The margin sites were inhabited by mostly opportunistic and contaminant-tolerant taxa, reflecting the elevated sediment contamination and total organic carbon (TOC) levels at those sites. Impacted samples from both assemblages had significantly higher sediment contaminant concentrations (mixtures) than reference samples, and degrees of impact were significantly correlated with increasing sediment contamination. However, due to the covariance between TOC and most sediment contaminants in the Estuary margins, it was concluded that both sediment contamination mixtures and elevated TOC contributed to the changes in benthos at the Estuary margin sites.

The same assessment methods were subsequently applied to samples from San Pablo Bay, Napa and Petaluma rivers, and three sites in the Napa-Sonoma Marsh in 2000–2001 (Thompson and Lowe, 2003). Only 8.3% of the samples from San Pablo Bay were impacted, and 67% of the margin samples from Napa River and Napa-Sonoma marsh were impacted. The high incidence of benthic impacts at the Estuary margin sites was consistent with the results described above for the entire Estuary, and was also most closely related to elevated TOC concentrations and elevated sediment contamination mixtures, including organophosphate and pyrethroid pesticides. Elevated TOC and sediment contamination in those samples had more influence on benthic species composition and abundances than did differences in hydrodynamic regime (e.g., river or marsh channel), or seasonal and tidal differences in salinity, flow, turbidity, or temperature. Sediments from the same sites were used to study their effects on the clam *Macoma nasuta* in laboratory exposures (Werner et al., 2004). Mortality, stress proteins (hsp70) in gill tissues, tissue lesions in gonads, and lysosomal membrane damage were significantly correlated with clam tissue concentrations of DDT and/or its metabolites. Tissue concentrations of Ni, Cr, and Cu were associated with macrophage aggregates in digestive gland and germ cell necrosis; Cd was linked to mortality and lysosomal damage.

In summary, biological impacts of Ag and Cd to several localized clam populations has been shown. Cu ions in sediment were toxic to mussel larvae, and affect the reproductive activity of *Macoma*. Histopathologic and enzymatic biomarkers have shown impacts on clams along a combined metal gradient in the northern reach of the Bay. Se does not appear to be toxic to the benthic invertebrates of the Bay, but invertebrates play an important role in transfer of Se in the food web. Cr, Ni, and V do not appear to have direct effects on the benthos. Impacts of sediment contaminant mixtures on some benthic assemblages have been shown. Clearly, much more information on other organisms and contaminants are needed.

2.3. Fish

The San Francisco Estuary has a diverse fish fauna and as many as 90% of species in the commercial and recreational fisheries use the Bay at some stage of their life cycle. The Bay is important for Chinook (*Oncorhynchus tshawytscha*) and Coho salmon (*O. kisutch*), Pacific herring (*Clupea pallasi*), Pacific and California halibut (*Hippoglossus stenolepis* and *Paralichthys californicus*), starry flounder (*Platichthys stellatus*), English sole (*Pleuronectes vetulus*), sturgeon (*Acipenser* spp.), surfperches (Embiotocidae), northern anchovy (*Engraulis mordax*) and Pacific sardines (*Sardinops sagax caeruleus*), to mention a few (Baxter et al., 1999). San Francisco Bay also has a large urban recreational fishery (Karpov et al., 1995). In the very large watershed of the Estuary there are more than 50 freshwater fish species (Moyle, 2002). Many of those in the Estuary and its catchment are in decline (Brown et al., 1994; Moyle, 1994; Meng et al., 1994) with contamination, climate change, invasive species, habitat alteration and harvesting as the main potential causes of the declines.

As is the case with many contaminated coastal and estuarine systems, the extent of contaminant effects on fish in this system is not well understood because there have not been enough studies of long-term, low-level exposures to contaminants (e.g., Forrester et al., 2003). However, progress has been made in the last 30 years and, based on available evidence cited below, contaminants are having some effects on fish although the consequences for fish populations are highly uncertain.

Extensive bioassay testing of fish with sediments and water from the Estuary has been carried out, but their results generally do not appear in the peer-reviewed literature. As these approaches generally do not lend themselves to deriving strong conclusions because of their insensitivity to subtler effects of contaminations, we focus here on and field-based studies of fish health that are more appropriate for assessing the influence of contaminants. Lethal effects of contaminants on adult fish are suspected in some isolated instances, such as periodic kills of striped bass (*Morone saxatilis*) (Brown et al., 1987), but it is more likely that survival of larval fish and long-term effects of chronic contaminant exposure on adults are involved in any effects on fish populations.

Pesticides released in the watershed from agricultural and home use have been investigated for their potential effects on several depleted fish species. In the Sacramento River, Bennett et al. (1995) found that 26–30% of the larval striped bass captured in 1988–1990 had alterations of the liver consistent with exposure to toxic compounds and this percentage dropped significantly after control measures were later adopted for runoff from rice farming. This study showed the potential for an interaction between food supply and toxicity and pointed to the potential for toxic impacts to be masked by variability in other factors. Bailey et al. (1995) reported acute toxicity to striped bass larvae in runoff water to the Sacramento River. In a test to determine the effects of runoff after experimental application of diazinon and esfenvalerate to an orchard, Sacramento splittail (*Pogonichthys macrolepidotus*) larvae showed only subtle changes in histology after a 96-h exposure, but experienced significant mortality and growth reductions within 90 days (Teh et al., 2005), indicating that long-term exposures to orchard runoff have the potential to affect normal development and survival of juvenile fish. These data also showed that examining effects after 96 h, as occurs in regulatory compliance toxicity testing, might miss significant longer-term effects. In another Delta fish species, the delta smelt (*Hypomesus transpacificus*) the spawning habitat was shown to have elevated concentrations of several pesticides in 1999–2000, but in 1998 the high spring outflows resulted in greatly reduced pesticide concentrations (Kuivila and Moon, 2004).

Sacramento sucker (*Catostomus occidentalis*) kept in cages during winter runoff events (after pesticide application) in the San Joaquin River had greater frequency of DNA strand breaks compared to fish at a reference site (Whitehead et al., 2004).

Concentrations of pyrethroid pesticides (e.g., permethrin, cypermethrin, esfenvalerate, bifenthrin, and cyfluthrin, the five most commonly used in the Central Valley of California), which are rapidly replacing organophosphates, were found to be in the 0–97 ng L^{-1} range in water (Bacey et al., 2005) and in the low ng g^{-1} in sediments (Weston et al., 2004). The maximal water concentrations in this study are close to those found to have effects on immune suppression (Clifford et al., 2005). In that study juvenile Chinook salmon exposed to 100 ng g^{-1} esfenvalerate in sediment had reduced time to death compared to the controls after a challenge with hemapoetic viral necrosis virus.

There is very little published information on whether the PAHs in the Bay are affecting fish. Gunther et al. (1997) found induction of ethoxyresorufin-*O*-deethylase (EROD) activity in speckled sanddabs (*Citharichthys stigmaeus*) exposed to sediments taken from near an old refinery effluent disposal site. In the 1980s, starry flounder captured near Berkeley in San Francisco Bay had poorer reproductive success when spawned in the laboratory than those captured at a site in San Pablo Bay with the former site having higher concentrations of fluorescent compounds in the bile as well as PCBs in the eggs (Spies and Rice, 1988).

Average concentrations (dissolved) of PAHs in water range between 20 and 120 ng L^{-1} in various the segments of the Estuary (Ross and Oros, 2004). Toxic effects have been noted in developing Pacific herring and pink salmon (*Oncorhynchus gorbuscha*) exposed to PAH concentrations in the low ppb range (Carls et al., 1999; Heintz et al., 1999). There also is evidence in Japanese medaka (*Oryzias latipes*) (Rhodes et al., 2005) of toxicity at low-ppb concentrations during development. While concentrations in water about two orders of magnitude greater are needed to elicit effects based on these literature values, concentrations in sediments are higher (in the range of 31–230 mg kg TOC^{-1}; Oros and Ross, 2004) relative to concentration thresholds associated with effects in coastal sediments (Long and Morgan, 1991).

Studies of biomarkers in fish from the Estuary have revealed effects of contaminants on a variety of cellular processes and tissue structure. However, in these studies it is often difficult to associate particular contaminants with effects, and the biomarkers could be responding to a mixture of contaminants. Livers of white croakers (*Genyonemus lineatus*) and starry flounders from San Francisco Bay had a greater incidence of hydropic vacuolation of biliary epithelial cells than those from Bodega Bay, and this condition was statistically associated with sediment and tissue concentrations of PAHs or their metabolites and with several chlorinated hydrocarbons (e.g., PCBs and DDTs; Stehr et al., 1997).

Several studies have established the strong possibility that populations of fish in the Estuary are extensively affected by reproductive toxins that interfere with normal sexual determination, such as egg development in females and successful reproduction. In the mid-1980s the starry flounder, which is now not as common in the Estuary as it was 30 years ago, was shown to be reproductively impaired in the mid-Bay region near Berkeley compared to San Pablo Bay (Spies and Rice, 1988). Females from Berkeley had elevated mixed-function oxidases (i.e., P4501A) during the spawning season compared to those from San Pablo Bay (Spies et al., 1988), and the mixed function oxidase activities of females collected near Berkeley and spawned in the laboratory were inversely related to several measures of reproductive success (fertilizable eggs, fertilization success and normal development through hatching) (Spies and Rice, 1988). The concentrations of PCBs in eggs were correlated with the poorer hatching success of fertilized eggs. Setzler-Hamilton et al. (1988) reported that concentrations of mononuclear aromatic hydrocarbons, alicyclic hexanes, and DDTs in striped bass were correlated with egg resorption, abnormal egg maturation, and egg death.

Aside from the implications of these reproductive studies, nothing has been published on studies that have been carried out on endocrine disruption of fish in San Francisco Bay related to the elevated concentrations of

PCBs, steroids, alkylphenols, and a variety of pesticides found in the Estuary. There is a growing awareness of this problem in fish (e.g., Jobling et al., 1998; Kime, 1998). Estrogen and other steroids have been documented in California in effluent from sewage treatment plants, near cattle feed lots, and from aquaculture facilities (Kolodziej et al., 2003, 2005).

Besides steroids that are passed from humans through sewage, other pharmaceuticals have been documented in freshwater streams, estuaries and coastal waters (e.g., Halling-Sorenson et al., 1998), and they may pose a hazard (Daughton and Ternes, 1999), especially in an Estuary with multiple contaminants present (Laville et al., 2004). Although preliminary indications are that waterborne concentrations of many pharmaceuticals are about 2 orders of magnitude greater than the thresholds for effects observed in laboratory studies, not nearly enough is known to determine the threat from these contaminants in surface waters (Fent et al., 2006). Virtually nothing has been done with these emerging contaminants in the Estuary and its watershed.

2.4. Birds

The San Francisco Estuary is an important element of the Pacific flyway for migratory birds (Goals Project, 1999). The Estuary is home to 281 species of birds that use its aquatic habitats; 25% of the flyway waterfowl population and a million shorebirds each year spend the winter there (Goals Project, 1999, Stenzel et al., 2002). The Bay is particularly important for Pacific flyway populations of canvasbacks (*Aythya valisineria*), greater and lesser scaup (*A. marila* and *A. affinis*), and surf scoters (*Melanitta perspicillata*) that winter in the Estuary (Trost, 2002; USFWS, 2002). California gull (*Larus californicus*) and double-crested cormorant (*Phalacrocorax auritus*) populations appear to be expanding in the Estuary, while Forster's and Caspian terns (*Sterna forsteri* and *S. caspia*) as well as diving ducks have been gradually declining (Strong et al., 2004; Warnock et al., 2002).

Exposure of birds to contamination in the Estuary has largely been assessed by examination of accumulation in tissues and eggs during the nesting season, but also in tissues of wintering waterfowl and in prey items. Although exposures to non-bioaccumulative chemicals may occur, it is generally recognized that ingestion of prey items that contain persistent bioaccumulative chemicals (i.e., dietary exposure) represents the greatest risk for birds. Toxicological effects may be deduced by comparing concentrations measured in tissues or eggs to known contaminant-effect thresholds determined in laboratory studies. Contaminants may affect avian reproduction through direct impacts to the developing embryo (from contaminants accumulated in albumen or yolk of eggs), compromises in shell quality, altered behavior of the incubating adult, contaminant-induced growth reductions, and impaired post-hatch survival of juveniles. Methylmercury, Se, organochlorine pesticides, PCBs, and dioxins are known to accumulate to embryotoxic concentrations in eggs of birds in the wild (Hoffman et al., 1996; Thompson, 1996; Heinz, 1996).

Currently, Hg is the contaminant of greatest concern for birds in the Estuary. Concentrations are elevated above effect levels in the eggs of various species that utilize the ecosystem for reproduction. Hg concentrations ranged between <0.02 and $3.33\,\mu g\,g^{-1}$ (wet weight) in eggs from 15 species collected in 2000–2001 throughout the Estuary and Delta (Schwarzbach and Adelsbach, 2003). The currently accepted lowest observed adverse effect level (LOAEL) for Hg in avian eggs is $0.5\,\mu g\,g^{-1}$ (wet weight) (range 0.5–$1.0\,\mu g\,g^{-1}$ ww) as determined from multigenerational feeding studies in ring-necked pheasants (*Phasianus colchicus*) and mallards (*Anas platyrhynchos*) (Fimreite, 1971; Heinz, 1976). In the Estuary and the Sacramento-San Joaquin River Delta, the degree of piscivory and location of feeding areas strongly influenced egg Hg patterns. The highest concentration observed in the Estuary was found in Forster's terns nesting at a South Bay salt pond and the lowest level was found in western and California gulls (*Larus occidentalis* and *L. californicus*). Of further note is the fact that 75–90% of Forster's and Caspian tern eggs collected from the Estuary were above the current LOAEL for impacts to avian reproduction. However, the California clapper rail (*Rallus longirostris obsoletus*) was most likely at greatest risk from egg Hg accumulation. The non-migratory, small home range life history strategy of the rail and its dependence on tidal salt marsh in the Estuary put it at surprisingly high risk from Hg relative to its generally low trophic position in these foodwebs. This is likely to be a direct result of methylmercury production and transport in these salt marshes. Double-crested cormorants, great blue herons (*Ardea herodias*), and great egrets (*A. alba*) nesting in the Delta did not appear to be at risk of Hg-induced hatching failure. The double-crested cormorant feeds in the deeper regions of the Estuary. This may be the main reason Hg concentrations in cormorants are below those seen in terns collected from nearby areas. Lower concentrations observed in egrets and herons are due to the fact that they are facultative piscivores and also feed on nearshore invertebrates (amphibians, crayfish, etc.) and on upland terrestrial mammals and birds.

Hepatic microsomal EROD activities of double-crested cormorant embryos collected in the Estuary in 1993–1994 were four to eight times higher than at a reference site in Oregon (Davis et al., 1997). The authors concluded that cormorant embryos in the Estuary were exposed to concentrations of dioxin-like compounds at the threshold for toxic effects in cormorants. Although most of the cormorants displayed a consistent dose-response profile, there was substantial variation in EROD activity among individuals and populations of cormorants, and a few individuals were uninduced.

Eleven-day-old nestlings and pipping embryos of black-crowned night-herons (*Nycticorax nycticorax*) collected from Bair Island and West Marin Island showed that aryl hydrocarbon hydroxylase and benzyloxyresorufin-*O*-dealkylase activities were only slightly elevated when compared with birds from a reference site in Virginia (Rattner et al., 1996). The elevated levels corresponded with elevated organochlorine pesticides and total PCBs at the site and in concurrently collected eggs and pipping embryos. Pollutant concentrations of nestlings were rarely associated with monooxygenase activity. In contrast, concurrently collected pipping heron embryos (often siblings of the nestlings) exhibited pronounced monooxygenase induction (sometimes more than 25-fold). Monooxygenase activity of pipping embryos was significantly correlated with total PCBs, aryl hydrocarbon receptor-active PCB congeners, and toxic equivalents.

Adult male greater scaup, surf scoters, and ruddy ducks (*Oxyura jamaicensis*) collected from Carquinez Strait and Tomales Bay (March 1989) showed significant relationships between increasing hepatic Hg concentrations and lower body, liver, and heart weights; decreased hepatic glutathione concentration, glucose-6-phosphate dehydrogenase, and glutathione peroxidase activities; increased ratio of oxidized glutathione to reduced glutathione; and increased glutathione reductase activity (Hoffman et al., 1998). With increasing hepatic Se concentrations, glutathione peroxidase increased, but reduced glutathione decreased. Hepatic Se concentrations were highest in scaup (geometric mean = $67\,\mu g\,g^{-1}$ dry weight) and scoters ($119\,\mu g\,g^{-1}$) from Carquinez Strait, whereas hepatic Hg was highest ($19\,\mu g\,g^{-1}$) in scaup and scoters from Tomales Bay. Concentrations of Hg and Se and the metabolic variables affected have also been associated with adverse effects on reproduction and neurological function in experimental studies with mallards (Hoffman and Heinz, 1998). Body weight of adult male surf scoters from six locations in San Francisco Bay (January, March 1985) also was significantly negatively associated with Hg concentrations in their livers (Ohlendorf et al., 1991), but not with concentrations of other trace elements or organochlorines.

Many studies have shown interactions between Se and Hg or other inorganic elements, but the interactions are complex and influenced by many factors. A brief summary is provided here with reference to San Francisco Bay waterfowl, but readers are encouraged to consult other references (e.g., Heinz and Hoffman, 1998; reviews by Culvin-Aralar and Furness, 1991 and by Ohlendorf, 1993, 2003) for more details on this topic. Although Se and Hg concentrations in the livers of various free-living carnivorous mammals often are highly correlated in a molar ratio of 1:1, there is no consistent pattern for such a correlation in the livers of birds. For example, hepatic Se and Hg were correlated, with an overall Se:Hg molar ratio of 6:1, in surf scoters and greater scaups from San Francisco Bay during 1982 (Ohlendorf et al., 1986). In a subsequent study of scoters sampled twice at six locations in the Bay during 1985, Se and Hg in the livers were not correlated; Se-to-Hg ratios were typically between 7:1 and 15:1 for most locations and collection times, but the mean ratio at one site was 45:1 (Ohlendorf et al., 1991).

Interactive effects of Se with Hg have been evaluated in a reproductive study with mallards, which were fed Se or Hg alone or both Se and Hg together (Heinz and Hoffman, 1998). Se and Hg each caused significant adverse effects on reproduction when present alone in the diet at higher treatment levels. However, when the diet contained 10 mg Se/kg plus 10 mg Hg/kg, the effects on reproduction were worse than for either Se or Hg alone. The number of young produced per female and frequency of teratogenic effects were significantly affected by the combination of Se and Hg in the diet, and Hg also enhanced the storage of Se in duck tissues.

Black-crowned night-heron eggs collected from Bair Island in 1982 showed that eggshell thickness and thickness index were negatively correlated with DDE concentrations in the eggs, and were significantly lower than historical means for San Francisco Bay eggs (Ohlendorf et al., 1988). Night-heron eggs collected from Bair Island and other Estuary sites (1982–1983) showed that DDE concentrations in 16% of eggs were higher than those associated with reduced reproductive success in the night-herons ($8\,\mu g\,g^{-1}$ wet weight, Ohlendorf and Marois, 1990). No obvious anomalies or skeletal defects were detected in pipping embryos, but embryo weight was significantly less at Bair Island when compared to embryos from captive controls at the Patuxent Wildlife Research Center (Maryland). PCB concentrations in the eggs collected from Bair Island ranged from 0.75 to $52\,\mu g\,g^{-1}$ wet weight (Hoffman et al., 1986), and were inversely related to embryonic weight; crown-rump length was significantly lower in Bair Island embryos when compared to controls.

Continuing evidence of the effects of DDE on eggshell quality was found when night-heron and snowy egret (*Egretta thula*) eggs were collected from several nesting sites in the Estuary during 1989–1991 (Hothem et al., 1995). There was some evidence of impaired reproduction (e.g., cracked or dented eggs), and developmental anomalies were observed in 2 of 18 embryos that failed to hatch at Alcatraz; one deformed chick also was found at that site. However, contaminant concentrations (inorganic trace elements, organochlorine pesticides, and PCBs) were generally below known effect thresholds, and egg predation appeared to limit reproductive success.

Black-necked stilt (*Himantopus mexicanus*) eggs collected from the Chevron Richmond Refinery's Water Enhancement (treatment) Wetland area (1994–1995) had Se concentrations (geometric mean = $25\,\mu g\,g^{-1}$ dry weight) that were high enough to cause a reduction in hatchability of some eggs (Ohlendorf and Gala, 2000; Ohlendorf et al., 1998, 2001). In 1997, a revised management approach changed the operation and configuration of the treatment wetland (e.g., increased vegetation density, deeper water, removal of nesting islands), and Se concentrations were significantly reduced in stilt eggs by 2000 (mean $< 8\,\mu g\,g^{-1}$).

Long-term studies of California clapper rail nest success and egg hatchability in six marshes in the North and South Bays have shown that hatchability of rail eggs in those marshes was depressed to 65 and 70%, respectively. Only 45% of the nests successfully hatched at least one egg (Schwarzbach et al., 2001, 2006). Contamination appeared to exert an adverse influence over clapper rail reproductive success as evidenced by the observation of deformities, embryo hemorrhaging, embryo malpositions, and reduced hatchability. Hg was the only contaminant common to all marshes and was the contaminant believed to be most likely producing the observed depression in rail egg hatchability. Hg exceeded avian embryotoxic threshold concentrations and was correlated with reduced hatchability. Half of the fail-to-hatch eggs from the South Bay were above the low adverse effects Hg concentration ($0.5\,\mu g\,g^{-1}$ wet weight for ring-necked pheasants; Fimreite, 1971), and 25% were above the guideline for mallards ($0.8\,\mu g\,g^{-1}$ wet weight; Heinz, 1976). In the North Bay, 20% of failed eggs were above the pheasant threshold and 7% were above the duck threshold. Organochlorine and PCB concentrations in the eggs were below effect thresholds. Flooding was a minor factor, reducing the number of eggs available to hatch by only 2.3%, but predation on eggs was a major factor in reducing nest success, reducing eggs available to hatch by a third.

2.5. Marine mammals

Marine mammals are generally relatively long-lived, maintain substantial fat stores (which sequester lipophilic compounds), and may have poor metabolic (detoxification) and excretory capabilities for these pollutants; thus, they represent the ultimate biological "sink" for many persistent pollutants (Brooks, 1974; Hutzinger et al., 1974; Tanabe et al., 1988, 1994). Organohalogen and PAH contaminants could be especially important, and have been suggested as factors altering health in several marine mammal species. Tissue residues of PCBs, DDTs, PBDEs, and PAHs have been associated with various physiological disorders in several marine mammal species, including reproductive, endocrine, and immunological alterations (Reijnders, 1980; Addison, 1989; Martineau et al., 1994; Tanabe et al., 1994; De Guise et al., 1995; Lahvis et al., 1995; Beckmen et al., 2003; Hall et al., 2003; Jenssen et al., 2003). Experimental studies supporting these field observations demonstrated depressed plasma retinol and thyroid hormone levels, implantation failure, and a suite of altered immunological parameters, in captive harbor seals fed environmentally contaminated fish (Reijnders, 1986; Brouwer et al., 1989; De Swart et al., 1996; Ross et al., 1996; Van Loveren et al., 2000). Taken together, these investigations support a hypothesis of contaminant-induced reproductive and immunological impairment in marine mammals—phenomena that may have contributed to the high mortality observed in several marine mammal populations during past morbillivirus epizootics (Hall et al., 1992; Aguilar and Borrell, 1994).

Marine mammals found in the San Francisco Estuary include California sea lion (*Zalophus californianus*), Pacific harbor seal (*Phoca vitulina richardii*), harbor porpoise (*Phocoena phocoena*), gray whale (*Eschrichtius robustus*), and southern sea otter (*Enhydra lutris nereis*). River otters (*Lontra [formerly Lutra] canadensis*) and muskrats (*Ondatra zibethica*) inhabit the delta and tidal salt marshlands. Several studies have quantified contaminant residue levels in Estuary mammals. Concentrations in gray whale, harbor seal, California sea lion, and sea otter have generally been as high as or higher than in the same species elsewhere (Risebrough et al., 1980; Varanasi et al., 1994; Kopec and Harvey, 1995; Nakata et al., 1998, Young et al., 1998; Bacon et al., 1999; Kajiwara et al., 2001; She et al., 2002; Neale, 2004; Neale et al., 2005a, 2005c). Among Estuary marine mammals, the harbor seal—the most common marine mammal in the Estuary and the only year-round resident—is the only species for which biological effects of contaminants have been investigated.

Observations of premature parturition in Estuary harbor seals led to an early report on impacts of anthropogenic pollutants, which documented relatively high concentrations of persistent organic and metal contaminants in seal tissues from the late 1960s and 1970s (Risebrough et al., 1980). Nevertheless, disturbance of seals at haul-out sites was considered of greater concern, given that seal numbers appeared stable and pup production normal at the time. Renewed concern arose from the observation that while numbers of harbor seals off the west coast of North America had steadily increased during the 1970s–1980s, the San Francisco Estuary population had not (Fancher and Alcorn, 1982; Allen et al., 1989; Harvey et al., 1990; Stewart and Yochem, 1994). The first major investigation of contaminants in Estuary seals included standard hematology, serum retinol and thyroxin, and blood/plasma contaminant residues (DDE, PCBs, chlordane, Cd, Cu, lead, Hg, Ni, Se, and Ag). Organochlorine levels were relatively high: average plasma DDE was 12.6 ppb wet weight (ww), 14.3 ppm lipid weight (lw); average whole blood PCB (Arochlor 1260) was 47 ppb ww, 58 ppm lw (Kopec and Harvey, 1995). The sum of individual PCB congeners (up to 20) in whole blood samples averaged 50.5 ppb ww (Young et al., 1998); this was greater than ΣPCB blood residues of experimental harbor seals fed contaminated fish (referenced above). All blood Hg and Se residues exceeded human toxicity thresholds, and a small percentage of seals had Cd and lead residues exceeding these limits (ATSDR, 1989a, b, 1990a, b; Fan and Chang, 1991; Kopec and Harvey, 1995).

Although health indices (serum chemistries, retinol and hormone levels) were not compared directly to contaminant levels in individuals, average serum retinol and erythrocyte parameters were found to be somewhat depressed, and white cell counts elevated, compared to published values for this species elsewhere (Kopec and Harvey, 1995). Collectively, the data suggested the possibility of contaminant-induced anemia, leukocytosis and disruption of Vitamin A dynamics in this population.

Recent field-based studies have focused on persistent contaminants and contaminant-related immune and health alterations in the harbor seal, including the Estuary population. In the first large study ($n = 190$) of its kind, seals from central California were found to have considerably higher blood levels of PCBs, DDE, and PBDEs as compared to a reference population (Bristol Bay, Alaska), and contaminant levels in California seals were correlated with different demographic and environmental factors than for Alaska seals (Neale, 2004). Levels of these organohalogens in harbor seal pups from the central California coast and San Francisco Estuary correlated positively with duration of nursing, demonstrating the importance of lactational transfer of pollutants in this at-risk population (Neale et al., 2005c). In a study focused on contaminant-induced health alterations in the Estuary harbor seal population, relationships between contaminant exposure and several key hematological parameters were examined and current PCB levels were compared with levels determined in Estuary seals a decade earlier (Neale et al., 2005a). PCB residues in harbor seal blood apparently decreased during the past decade, but remained at levels great enough that adverse reproductive and immunological effects might be expected. A positive association was observed between leukocyte counts and blood levels of PBDEs, PCBs, and DDE in seals, and an inverse relationship between red blood cell count and PBDEs. Although not necessarily pathologic, these responses were viewed as sentinel indications of contaminant-induced alterations in harbor seals of the San Francisco Estuary, which, in individuals with relatively high contaminant burdens, might include increased rates of infection and anemia.

Experimental studies of immune function have begun to shed light on marine pollutant immunotoxicity in the harbor seal. The removal of pathogens from the body involves the concerted participation of components of both innate and adaptive immunity and is largely dependent on the processes of lymphocyte activation, proliferation, and differentiation into armed effector and memory cells (reviewed in Weiss and Littman, 1994; Kung and Thomas, 1997; Qian and Weiss, 1997; Janeway et al., 1999; Abbas and Lichtman, 2003). In turn, lymphocyte activation via antigen receptor signaling is dependent on initiation and propagation of intracellular signaling by protein tyrosine kinases (PTKs), and subsequent cellular responses—proliferation, differentiation, and intercellular communication—are subject to control by cytokines. Recently, harbor seal T lymphocytes exposed in vitro to model PAH (benzo[a]pyrene; BaP) and PCB (chlorinated biphenyl CB-80 and CB-156) compounds were found to exhibit suppressed proliferative responses to mitogen (Neale et al., 2002). A follow-up study explored potential mechanisms underlying this effect via analysis of the relative genetic expression of PTKs and cytokines that play key roles in T-cell activation, initiation of adaptive immune responses, and macrophage function (Neale et al., 2005b). In vitro exposure of mitogen-stimulated harbor seal leukocytes to BaP or CB-169 produced significantly altered genetic expression in all targets—PTKs Fyn (of the Src family of kinases) and Itk (the murine "inducible T-cell kinase") and interleukins I (IL-1) and II (IL-2). These results suggested incomplete T-cell receptor signal transduction and impaired macrophage function, and the suppression of the T-cell growth factor, IL-2, indicated a mechanism consistent with the previously observed suppression of T-cell proliferation. Findings were in line with those of previous researchers working with model (rodent) organisms and human cell lines in supporting a hypothesis of contaminant-altered lymphocyte function mediated (at least in part) by disruption of lymphocyte receptor signaling and cytokine production (e.g., Clark et al., 1991; Archuleta et al., 1993; Steppan et al., 1993; Mounho and Burchiel, 1998). Collectively, experimental study results implied that extensive accumulation of these lipophilic pollutants by top-trophic-level marine mammals could lead to altered T-cell activation in vivo and impaired cell-mediated immunity against viral pathogens.

In conclusion, accumulating evidence indicates that certain compounds, particularly of the organochlorine and PAH classes of persistent organic contaminants, can have adverse effects on individual health of Estuary mammals. Disruption of lymphocyte signaling and altered cytokine production appear to be key aspects of PAH and PCB immunotoxicity, and the macrophage has also been suggested as a primary target; however, specific biochemical targets and mechanisms responsible for immunomodulation are still under investigation. New directions in sub-organismal research include application of novel molecular biomarkers to explore effects on potential cellular targets of bioactive xenobiotics (Neale et al., 2004, 2005b). However, the generalization of findings at the cellular and organismal levels of organization to population-level phenomena remains controversial (O'Shea and Brownell, 1998; O'Shea, 2000; Ross et al., 2000), and the need for long-term monitoring of environmental contamination and population dynamics of marine mammals in the Estuary is clear.

Lastly, while most research on Estuary pollutants and their effects in marine mammals has focused on persistent organic pollutants, increasing awareness of the potential toxicity of previously unidentified or unmonitored organic and inorganic contaminants should lead to expanded areas of research (e.g., Oros and David, 2002). For example, relatively high residues of heavy metals and Se residues have been found in marine mammals elsewhere (e.g., Wagemann et al., 1990; Lake et al., 1995; Fossi et al., 1997). Butyltins are another class of compounds found in marine mammals stranded along the California coast (Kajiwara et al., 2001) that may have immunotoxic effects (Nakata et al., 2002).

3. Discussion and conclusions

The studies summarized in this paper provide a body of evidence showing that biological impacts from exposure to specific contaminants have occurred in specific organisms in the San Francisco Estuary. These studies included laboratory and field studies on a variety of organisms and contaminants that resulted in biological effects at several levels of biological organization (sub-cellular through communities). However, the number of species (~15) and contaminants (<20) investigated represents a very small set of species and known contaminants of concern in the Estuary. More information was available for fish and birds than other groups, and only a few studies have been conducted on plankton, and for mammals other than harbor seals.

Impacts at lower levels or biological organization have the potential to affect higher levels of organization. Studies of biomarkers and cellular level impacts (e.g., endocrine disruption, enzyme induction, histopathology) indicate potential for organismal level impacts. However, few studies addressed linkages between sub-organismal effects and organismal health. Similarly, studies of impacts on individual organisms (e.g., reproductive impairment, growth) suggest possible impacts on populations, but such linkages have not been addressed.

Only a few studies showed that population or community declines were linked to contamination. These included localized reproductive impacts on the clams *Macoma* and *Corbula* due to elevated concentrations of Ag, changes in macrobenthic assemblage species composition related to contaminant mixtures in sediment, and decreased hatchability in California clapper rails due to Hg exposure.

Impacts from exposure to contaminants are but one of the numerous factors that may affect organisms and populations. Previous studies in the San Francisco Estuary have suggested that population declines of several organisms were related to the frequency and duration of the Estuary mixing zone resulting from fresh water inflows (Jassby et al., 1995). Striped bass fluctuations have been related to oceanic conditions (Bennett et al., 1995). However, diving ducks and shiner perch declines have been documented in the Estuary, but their declines have not been linked to specific causes. Ascribing a specific cause to recent increases in phytoplankton (Cloern et al., 2006) and decreases in pelagic organisms in the Delta (e.g., Bennett, 2005) has been difficult, and current hypotheses include multiple factors. Thus, the ability to ascribe cause for any biological impact is difficult and not unique to research on contamination, and will continue to be a major challenge to identify biological impacts of contamination.

3.1. Advances in understanding

Since the RMP began in 1993, there has been a shift in emphasis from a focus on potential impacts of trace metals to the understanding that a broader range of contaminants may be causing impacts in the Estuary. Hg and PCBs are currently the two major contaminants of regulatory focus in the region. Hg effects on reproduction of the endangered clapper rails were summarized above, and PCBs were related to effects on starry flounders, Chinook salmon, harbor seals, cormorants, and night-herons. Total maximum daily loads (TMDLs) are being prepared for both contaminants and are intended to control their loadings to the Estuary. However, the PCB TMDL is responding largely to human health concerns for fish consumption. Other contaminants of concern include Cu, Ni, PAHs, and various pesticides, particularly the pyrethroids.

In response to the recognized need for more comprehensive biological effects monitoring, the RMP established the Exposure and Effects Pilot Study (EEPS) in 2002. The EEPS work group is currently conducting a set of pilot studies that include toxicity testing, benthos, fish, and bird indicators that may be incorporated into the Program to provide more thorough and rigorous biological assessments of contaminant impacts.

3.2. Priorities for additional information

There is a clear need for more information about biological effects of contamination on more species and for more contaminants in the Estuary. Effects are unstudied for many emerging contaminants, especially personal care products, PBDEs, and numerous pesticides that are used in the California Central Valley that drains into San Francisco Bay.

Ideally it would be most efficient to develop a coordinated research program to determine cause and effect of priority contaminants of concern on key organisms and populations, by testing a series of hypotheses. These studies would require integrated field and laboratory experiments, using a variety of methods and endpoints, to understand contaminant exposure, mechanisms of effects, and linkages between levels of biological organization that produce impacts on priority biological resources. These studies should also consider the confounding, or overriding influences of physical environmental factors, and other biological and ecological factors such as pathogens, natural toxins, and predation and competition.

Simulation models that can link physical and geochemical processes with biological impacts could be used to explore and validate exposure of organisms to specific chemical forms, in water and sediment, and through successive trophic-levels. The extension of existing water-quality (e.g., Wood et al., 1995) and food chain accumulation models (Gobas and Wilcoxon, 2005), and eventually biological effects models, could test conceptual models and identify and prioritize information gaps that currently restrict a broad-scale quantitative assessment of contaminant effects on the estuarine ecosystem.

From a regulatory perspective, it is a high priority of both US EPA and California's state water resources control board (SWRCB) to develop regulatory biological criteria. Biocriteria, required by the CWA, are narrative descriptions or numerical values adopted into state or tribal water quality standards that can be used to factually and quantitatively describe a desired condition for the aquatic life in waters with a designated aquatic life use (US EPA, 1998). As presented in the Introduction, other agencies also have mandates to preserve and protect biological resources in the region. Thus, biological effects indicators that can be reliably used as biocriteria are needed.

The SWRCB is currently developing regulatory sediment quality objectives (SQO) for bays and estuaries that include biological criteria (SWRCB, 2006). The SQOs will use indicators from multiple lines of evidence that include sediment contaminants, toxicity, benthic macrofauna and human health impacts from fish consumption. The SQOs will be narrative objectives that protect aquatic life and human health. Where sediment impacts are identified, management actions to control anthropogenic contamination will depend on identifying the specific contaminants or mixtures of contaminants that may be causing the observed impacts on beneficial uses. Therefore, one of the most urgent needs is to link-specific contaminants to biological effects.

Advancing the understanding of biological effects in the San Francisco Estuary will probably come from the efforts of the several agencies and organizations working in the region. Each institution conducting research is currently responding to its respective mandates and priorities. The interpretation and synthesis of the knowledge and understanding about biological effects of contamination is an objective of the RMP, which will probably continue to serve that important function in the future.

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References

Abbas, A.K., Lichtman, A.H., 2003. Cellular and Molecular Immunology, fifth ed. Saunders, Philadelphia.

Addison, R.F., 1989. Organochlorines and marine mammal reproduction. Can. J. Fish. Aquat. Sci. 46, 360–368.

ATSDR, 1989a. Toxicological profile for mercury. Agency for Toxic Substances and Disease Registry, US Public Health Service. Contract No. 2005-88-608.

ATSDR, 1989b. Toxicological profile for selenium. Agency for Toxic Substances and Disease Registry, US Public Health Service. Contract No. 205-88-0608.

ATSDR, 1990a. Toxicological profile for lead. Agency for Toxic Substances and Disease Registry, US Public Health Service. Contract No. 68-C8-0004.

ATSDR, 1990b. Case studies in environmental medicine. Agency for Toxic Substances and Disease Registry, US Public Health Service.

Aguilar, A., Borrell, A., 1994. Abnormally high polychlorinated biphenyl levels in striped dolphins (*Stenella coeruleoalba*) affected by the 1990–1992 Mediterranean epizootic. Sci. Total Environ. 154, 237–247.

Allen, S.G., Huber, H.R., Ribic, C.A., Ainley, D.G., 1989. Population dynamics of harbor seals in the Gulf of the Farallones, California. Calif. Fish Game 75, 224–232.

Anderson, B., Hunt, J., B. Phillips, B., Thompson, B., Lowe, S., Taberski, K., Carr, R., 2006. Patterns and trends in sediment toxicity in the San Francisco Estuary. Environ. Res.

Archuleta, M.M., Schieven, G.L., Ledbetter, J.A., Deanin, G.G., Burchiel, S.W., 1993. 7,12-dimethylbenz[a]anthracene activates protein-tyrosine kinases Fyn and Lck in the HPB-ALL human T cell line and increases tyrosine phosphorylation of phospholipase C-γ1, formation of inositol 1,4,5-triphosphate, and mobilization of intracellular calcium. Proc. Natl. Acad. Sci. 90, 6105–6109.

Bacey, J., Spurlock, F., Starner, K., Feng, J., Hsu, J., White, J., Tran, D.M., 2005. Residues and toxicity of esfenvalerate and permethrin in water and sediments, in tributaries of the Sacramento and San Joaquin Rivers, California, USA. Bull. Environ. Contam. Toxicol. 74, 864–871.

Bacon, C.E., Jarman, W.M., Estes, J.A., Simon, M., Norstrom, R.J., 1999. Comparison of organochlorine contaminants among sea otter (*Enhydra lutris*) populations in California and Alaska. Environ. Toxicol. Chem. 18, 452–458.

Bailey, H.C., Alexander, C., Digiorgio, C., Miller, M., Dorshov, S.I., Hinton, D.E., 1995. The effect of agricultural drainage on striped bass in California's Sacramento-San Joaquin drainage. Ecotoxicology 3, 1573–3017.

Baines, S.B., Fisher, N.S., 2001. Interspecific differences in the bioconcentration of selenite by phytoplankton and their ecological implications. Mar. Ecol. Prog. Ser. 213, 1–12.

Baines, S.B., Fisher, N.S., Doblin, M.A., Cutter, G.A., 2001. Accumulation of dissolved organic selenides by marine phytoplankton. Limnol. Oceanogr. 46, 1936–1944.

Baxter, R., Hieb, K., Deleon, S., Flemming, K., Orsi, J., 1999. Report on the 1980–1995 Fish, Shrimp, and Crab Sampling in the San Francisco Estuary, California. Interagency Ecological Program Technical Report 63.

Beck, N.G., Bruland, K.W., Rue, E.L., 2002. Short-term biogeochemical influence of a diatom bloom on the nutrient and trace metal concentrations in South San Francisco Bay microcosm experiments. Estuaries 25, 1063–1076.

Beckmen, K.B., Blake, J.E., Ylitalo, G.M., Stott, J.L., O'Hara, T.M., 2003. Organochlorine contaminant exposure and associations with hematological and humoral immune functional assays with damage as a factor in free-ranging northern fur seal pups (*Callorhinus ursinus*). Mar. Pollut. Bull. 46, 594–606.

Bennett, W.A., 2005. Critical Assessment of the Delta Smelt Population in the San Francisco Estuary, California. San Francisco Estuary and Watershed Science 3, Article 1.

Bennett, W.A., Ostrach, D.J., Hinton, D.J., 1995. Larval stripped bass condition in a draught-stricken Estuary: evaluating pelagic food web limitations. Ecol. Appl. 5, 680–692.

Brand, L.E., Sunda, W.G., 1986. Reduction of marine phytoplankton reproduction rates by copper and cadmium. J. Exp. Mar. Biol. Ecol. 96, 225–250.

Brooks, G.T., 1974. Chlorinated Insecticides: Technology and Application. CRC Press, Cleveland.

Brouwer, A., Reijnders, P.J.H., Koeman, J.H., 1989. Polychlorinated biphenyl (PCB)-contaminated fish induced vitamin A and thyroid hormone deficiency in the common seal (*Phoca vitulina*). Aquat. Toxicol. 15, 99–106.

Brown, L.R., Young, G., Nishioka, R.S., Bern, H., 1987. Preliminary report on the physiological status of striped bass in the Carquinez Strait die-off. Fish. Res. 6, 5–16.

Brown, L.R., Moyle, P.B., Yoshiyama, RM., 1994. Historical decline and current status of coho salmon in California. N. Am. J. Fish. Manage. 14, 237–261.

Brown, C.L., Parchaso, F., Thompson, J.K., Luoma, S.N., 2003. Assessing toxicant effects in a complex Estuary: a case study of effects of silver on reproduction in the bivalve, *Potamocorbula amurensis*, in San Francisco Bay. Hum. Ecol. Risk Assess. 9, 95–119.

Brown, C.L., Luoma, S.N., Parchaso, F., Thompson, J.K., 2004. Lessons learned about metals in the Estuary: the importance of long-term clam accumulation data. In: The Pulse of the Estuary. San Francisco Estuary Institute, Oakland, CA, pp. 38–45.

Buznikov, G.A., Nikitina, L.A., Bezuglov, V.V., Lauder, J.M., Padilla, S., Slotkin, T.A., 2001. An invertebrate model of the developmental neurotoxicity of insecticides: effects of chlorpyrifos and dieldrin in sea urchin embryos and larvae. Environ. Health Perspect. 109, 651–662.

Carls, M.G., Rice, S.D., Hose, J.E., 1999. Sensitivity of fish embryos to weathered crude oil, Part I: low level exposure during incubation causes malformations, genetic damage and mortality in larval Pacific herring (*Clupea pallasi*). Environ. Toxicol. Chem. 18, 481–493.

Clark, G.C., Blank, J.A., Germolec, D.R., Luster, M.I., 1991. 2,3,7,8-tetrachlorodibenzo-*p*-dioxin stimulation of tyrosine phosphorylation in B lymphocytes: potential role in immunosuppression. Mol. Pharmacol. 39, 495–501.

Clément, B., Cauzzi, N., Godde, M., Crozet, K., Chevron, N., 2005. Pyrene toxicity to aquatic pelatic and benthic organisms in single-species and microcosm tests. Polycyclic Aromatic Compounds 25, 271–298.

Clifford, M.A., Eder, K.J., Werner, I., Hedrick, R.P., 2005. Synergistic effects of esfenvalerate and infectioius hemapoetic necrosis virus on juvenile Chinook salmon mortality. Environ. Toxicol. Chem. 24, 1766–1772.

Cloern, J.E., 1996. Phytoplankton bloom dynamics in coastal ecosystems: a review with some general lessons from sustained investigation of San Francisco Bay, California. Rev. Geophys. 34, 127–168.

Cloern, J.E., Dufford, R., 2005. Phytoplankton community ecology: principles applied in San Francisco Bay. Mar. Ecol. Prog. Ser. 285, 11–28.

Cloern, J., Jassby, A., Schraga, T., Dallas, K., 2006. What is Causing the Phytoplankton Increase in San Francisco Bay? The Pulse of the Estuary. San Francisco Estuary Institute, Oakland, CA.

Conaway, C.H., Squire, S., Mason, R.P., Flegal, A.R., 2003. Mercury speciation in the San Francisco Bay Estuary. Mar. Chem. 80, 199–225.

Culvin-Aralar, L.A., Furness, R.W., 1991. Mercury and selenium interaction: a review. Ecotoxicol. Environ. Saf. 21, 348–364.

Daughton, C.G., Ternes, T.A., 1999. Pharmaceuticals and personal care products in the environment: agents of subtle change. Environ. Health Perspect. 17, 907–938.

Davis, J.A., Gunther, A.J., Richardson, B.J., O'Connor, J.M., Spies, R.B., Wyatt, E., Larson, E., Meiorin, E.C., 1991. San Francisco Estuary Project Status and Trends Report on Pollutants in the San Francisco Estuary. San Francisco Estuary Project, Oakland, CA, p. 291.

Davis, J.A., Fry, D.M., Wilson, B.W., 1997. Hepatic ethoxyresorufin-O-deethylase activity and inducibility in wild populations of double-crested cormorants (*Phalacrocorax auritus*). Environ. Toxicol. Chem. 16, 1441–1449.

Davis, J.A., McKee, L., Leatherbarrow, J., Daum, T., 2000. Contaminant loads from stormwater to coastal waters in the San Francisco Bay region: comparison to other pathways and recommended approach for future evaluation. Report to the State Water Resources Control Board, Sacramento, CA. San Francisco Estuary Institute, Oakland, CA, p. 82.

De Guise, S., Martineau, D., Beland, P., Fournier, M., 1995. Possible mechanisms of action of environmental contaminants on St. Lawrence beluga whales (*Delphinapterus leucas*). Environ. Health Perspect. 103, 73–77.

De Swart, R.L., Ross, P.S., Vos, J.G., Osterhaus, A.D.M.E., 1996. Impaired immunity in harbour seals (*Phoca vitulina*) fed environmentally contaminated herring. Vet. Q. 18, 127–128.

De Vlaming, V., 1996. Are the results of single species toxicity tests reliable predictors of aquatic ecosystem community responses? A review. Report of the State Water Resources Control Board, Sacramento, CA.

Donat, J.R., Lao, K.A., Bruland, K.W., 1994. Speciation of copper and nickel in South San Francisco Bay: a multi-method approach. Anal. Chim. Acta. 284, 547–571.

Edmunds, J.L., Kuivila, K.M., Cole, B.E., Cloern, J.E., 1999. Do herbicides impair phytoplankton primary production in the Sacramento-San Joaquin River delta? In: Morganwalp, D.W., Buxton, H.T. (Eds.), US Geological Survey Toxic Substances Hydrology Program—Proceedings of the Technical Meeting, Charleston, South Carolina, March 8–12, 1999—vol. 2—Contamination of Hydrologic Systems and Related Ecosystems. US Geological Survey Water-Resources Investigations Report 99-4018B, pp. 81–87.

Fan, A., Chang, L.M., 1991. Human exposure and biological monitoring of methylmercury and selenium. In: Dillon, H.K., Mat, H.H. (Eds.), Biological Monitoring and Exposure to Chemicals. Wiley, New York, pp. 223–241.

Fancher, L.E., Alcorn, D.J., 1982. Harbor seal census in South San Francisco Bay (1972–1977 and 1979–1980). Calif. Fish Game 68, 118–124.

Fent, K., Weston, A.A., Camminada, D., 2006. Ecotoxicology of human pharmaceuticals. Aquat. Toxicol. 76, 122–159.

Fimreite, N., 1971. Effects of dietary methylmercury on ring-necked pheasants with special reference to reproduction. Canadian Wildlife Service Occasional Paper No. 9, p. 39.

Fisher, N.S., Reinfelder, J.R., 1995. The trophic transfer of metals in marine systems. In: Tessier, A., Turner, D.R. (Eds.), Metal Speciation and Bioavailability in Aquatic Systems. Wiley, Chichester, pp. 363–406.

Fisher, N.S., Wang, W.X., 1998. Trophic transfer of silver to marine herbivores: a review of recent studies. Environ. Toxicol. Chem. 17, 562–571.

Fleeger, J.W., Carman, K.R., Nisbet, R.M., 2003. Indirect effects of contaminants in aquatic ecosystems. Sci. Total Environ. 317, 207–233.

Foe, C., 1995. Evaluation of the potential impact of contaminants on aquatic resources in the Central Valley and Sacramento-San Joaquin delta Estuary. Central Valley Regional Water Quality Control Board Report, Sacramento, CA.

Forbes, T.L., Forbes, V.E., Giessing, A., Hansen, R., Kure, L.K., 1998. Relative role of pore water versus ingested sediment in bioavailability of organic contaminants in marine sediments. Environ. Toxicol. Chem. 17, 2453–2462.

Forrester, G.E., Fredricks, B.I., Gerdeman, D., Evans, B., Steele, M.A., Zayed, K., Schweitzer, L.E., Suffet, I.H., Vance, R.R., Ambrose, R.F., 2003. Growth of estuarine fish is associated with the combined concentration of sediment contaminants and shows no adaptation or acclimation to past conditions. Mar. Environ. Res. 56, 423–442.

Fossi, M.C., Marsili, L., Junin, M., Castello, H., Lorenzani, J.A., Casini, S., Savelli, C., Leonzio, C., 1997. Use of nondestructive biomarkers and residue analysis to assess the health status of endangered species of pinnipeds in the south-west Atlantic. Mar. Pollut. Bull. 34, 163–170.

Gavis, J., Guillard, R.R.L., Woodward, B.L., 1981. Cupric ion activity and the growth of phytoplankton clones from different marine environments. J. Mar. Res. 39, 315–333.

Goals Project, 1999. Baylands Ecosystem Habitat Goals: A Report of Habitat Recommendations. US Environmental Protection Agency, San Francisco, California and San Francisco Bay Regional Water Quality Control Board, Oakland, CA.

Gobas, F.A., Wilcoxon, J., 2005. San Francisco Bay PCB food-web model. RMP Techical Report No. 90, San Francisco Estuary Institute, Oakland, CA, p. 68.

Gunther, A.J., Spies, R.B., Stegeman, J., Woodin, B., Carney, D., Oakden, J., Hain, L., 1997. EROD activity in fish as an independent measure of contaminant-induced mortality of invertebrates in sediment bioassays. Mar. Environ. Res. 44, 41–49.

Hall, A.J., Law, R.J., Harwood, J., Ross, M., Kennedy, S., Allchin, C.R., Campbell, L.A., Pomeroy, P.P., 1992. Organochlorine levels in common seals (*Phoca vitulina*) which were victims and survivors of the 1988 phocine distemper epizootic. Sci. Total Environ. 115, 145–162.

Hall, A.J., Kalantzi, O.I., Thomas, G.O., 2003. Polybrominated diphenyl ethers (PBDEs) in grey seals during their first year of life—are they thyroid hormone endocrine disrupters? Environ. Pollut. 126, 29–37.

Halling-Sorenson, B., Nielsen, S.N., Lanzky, P.F., Ingerslev, F., Holten Lutzhoft, H.C., Jorgensen, S.E., 1998. Occurrence, fate and effects of pharmaceuticals in the lithe environment—a review. Chemosphere 36, 357–393.

Hamilton, S.J., 1999. Hypothesis of historical effects from selenium on endangered fish in the Colorado River Basin. Hum. Ecol. Risk Assess. 5, 1153–1180.

Harvey, J.T., Brown, R.F., Mate, B.R., 1990. Abundance and distribution of harbor seals (*Phoca vitulina*) in Oregon, 1975–1983. Northwest Nat. 71, 65–71.

Heinz, G.H., 1976. Methylmercury: second-year feeding effects on mallard reproduction and duckling behavior. J. Wildl. Manage. 540, 82–90.

Heinz, G.H., 1996. Selenium in birds. In: Beyer, W.N., Heinz, G.H., Redmon-Norwood, A.W. (Eds.), Environmental Contaminants in Wildlife. CRC Press, Boca Raton, FL, pp. 447–458.

Heinz, G.H., Hoffman, D.J., 1998. Methylmercury chloride and selenomethionine interactions on health and reproduction in mallards. Environ. Toxicol. Chem. 17, 139–145.

Heintz, R.A., Short, J.W., Rice, S.D., 1999. Sensitivity of fish embryos to weathered crude oil, Part II: increased mortality of pink salmon (*Oncorhynchus gorbuscha*) embryos incubating downstream from weathered Exxon Valdez crude oil. Environ. Toxicol. Chem. 18, 494–503.

Herbold, B., Jassby, A.D., Moyle, P.B., 1992. Status and Trends Report on Aquatic Resources in the San Francisco Estuary. San Francisco Estuary Project, Oakland, CA, p. 257.

Hoffman, D.J., Heinz, G.H., 1998. Effects of mercury and selenium on glutathione metabolism and oxidative stress in mallard ducks. Environ. Toxicol. Chem. 17, 161–166.

Hoffman, D.J., Rattner, B.A., Bunck, C.M., Krynitsky, A., Ohlendorf, H.M., Lowe, R.W., 1986. Association between PCBs and lower embryonic weight in black-crowned night herons in San Francisco Bay. J. Toxicol. Environ. Health 19, 383–391.

Hoffman, D.J., Rice, C.P., Kubiak, T.J., 1996. PCBs and dioxins in birds. In: Beyer, W.N., Heinz, G.H., Redmon-Norwood, A.W. (Eds.), Environmental Contaminants in Wildlife. CRC Press, Boca Raton, FL, pp. 165–207.

Hoffman, D.J., Ohlendorf, H.M., Marn, C.M., Pendleton, G.W., 1998. Association of mercury and selenium with altered glutathione metabolism and oxidative stress in diving ducks from the San Francisco Bay Region, USA. Environ. Toxicol. Chem. 17, 167–172.

Hollibaugh, J.T., Wong, P.S., 1996. Distribution and activity of bacterioplankton in San Francisco Bay. In: Hollibaugh, J.T. (Ed.), San Francisco Bay: The Ecosystem. American Association for the Advancement of Science, Pacific Division, San Francisco, pp. 157–172.

Hornberger, M.I., Luoma, S.N., Cain, D.J., Parchaso, F., Brown, C.L., Bouse, R.M., Wellise, C., Thompson, J.K., 2000. Linkage of bioaccumulation and biological effects to changes in pollutant loads in South San Francisco Bay. Environ. Sci. Technol. 34, 2401–2409.

Hothem, R.L., Roster, D.L., King, K.A., Keldsen, T.J., Marois, K.C., Wainwright, S.E., 1995. Spatial and temporal trends of contaminants in eggs of wading birds from San Francisco Bay, California. Environ. Toxicol. Chem. 14, 1319–1331.

Hunt, J.W., Anderson, B.S., Phillips, B.M., Tjeerdema, R.S., Taberski, K.M., Wilson, C.J., Puckett, H.M., Stephenson, M., Fairey, R., Oakden, J., 2001. A large-scale categorization of sites in San Francisco Bay, USA, based on the sediment quality triad, toxicity identification evaluations, and gradient studies. Environ. Toxicol. Chem. 20, 1253–1265.

Hutzinger, O., Safe, S., Zitko, V., 1974. The Chemistry of PCBs. CRC Press, Cleveland, p. 269.

Janeway, C.A., Travers, P., Walport, M., Capra, J.D., 1999. Immunobiology: The Immune System in Health and Disease, fourth ed. Garland Publishing, New York, pp. 163–193.

Jassby, A.D., Powell, T.M., 1994. Hydrodynamic influences on interannual chlorophyll variability in an Estuary: upper San Francisco Bay-Delta. Estuaries Coast. Shelf Sci. 39, 595–618.

Jassby, A., Kimmerer, W., Monismith, S., Armor, C., Cloern, J., Powell, T., Schubel, J., Vendlinski, T., 1995. Isohaline position as a habitat indicator for estuarine populations. Ecol. Appl. 5, 272–289.

Jenssen, B.M., Haugen, O., Sormo, E.G., Skaare, J.U., 2003. Negative relationship between PCBs and plasma retinol in low-contaminated free-ranging gray seal pups (*Halichoerus grypus*). Environ. Res. 93, 79–87.

Jobling, S., Nolan, M., Taylor, C.R., Brighty, G., Sumpter, J.P., 1998. Widespread sexual disruption in wild fish. Environ. Sci. Technol. 32, 2498–2506.

Kajiwara, N., Kannan, K., Muraoka, M., Watanabe, M., Takahashi, S., Gulland, F., Olsen, H., Blankenship, A.L., Jones, P.D., Tanabe, S., Giesy, J.P., 2001. Organochlorine pesticides, polychlorinated biphenyls, and butyltin compounds in blubber and livers of stranded California sea lions, elephant seals, and harbor seals from coastal California, USA. Arch. Environ. Contam. Toxicol. 41, 90–99.

Karpov, K.A., Albin, D.P., Van buskirk, W.H., 1995. The marine recreational fishery in northern and central California—a historical comparison (1958–1986), status of stocks (1980–1986), and effects of changes in the California Current. Calif. Dept. Fish Game Fish. Bull. 176, 192.

Kime, D.E., 1998. Endocrine Disruption in Fish. Kluwer Academic Publishers, Dordrecht, the Netherlands, p. 416.

Klaassen, C.D., 2001. Casarett and Doull's Toxicology: The Basic Science of Poisons. McGraw-Hill Professional.

Kolodziej, E.P., Gray, J.L., Sedlak, D.L., 2003. Quantification of steroid hormones with pheromonal properties in municipal wastewater effluent. Environ. Toxicol. Chem. 22, 2622–2629.

Kolodziej, E.P., Harter, D., Sedlak, D.L., 2005. Dairy waste, aquaculture and spawning fish as sources of steroid hormones in the aquatic environment. Environ. Sci. Technol. 38, 6377–6384.

Kolpin, D.W., Furlong, E.T., Meyer, M.T., Thurman, E.M., Zaugg, S.D., Barber, L.B., Buxton, H.T., 2002. Pharmaceuticals, hormones and other organic wastewater contaminants in US streams, 1999–2000: a national reconnaissance. Environ. Sci. Technol. 36, 1202–1211.

Kopec, A.D., Harvey, J.T., 1995. Toxic Pollutants, Health Indices, and Population Dynamics of Harbor Seals in San Francisco Bay, 1989–1992. Moss Landing Marine Laboratories Techniques Publishers 96-4, ISSN:10808-2413.

Kuhn, A., Munns Jr., W.R., Serbst, J., Edwards, P., Cantwell, M.G., Gleason, T., Pelletier, M.C., Berry, W., 2002. Evaluating the ecological significance of laboratory response data to predict population-level effects for the estruarine amphipod *Ampelisca abdita*. Environ. Toxicol. Chem. 21, 865–874.

Kuivila, K.M., Foe, C.G., 1995. Concentrations, transport, and biological effects of dormant spray pesticides in the San Francisco Estuary, California. Environ. Toxicol. Chem. 14, 1141–1150.

Kuivila, K.M., Moon, G.E., 2004. Potential exposure of larval and juvenile delta smelt to dissolved pesticides in the Sacramento-San Joaquin Delta, California. Am. Fish. Soc. Symp. 39, 229–241.

Kung, C., Thomas, M.L., 1997. Recent advances in lymphocyte signaling and regulation. Frontiers Biosci. 2, 207–221.

Kuwabara, J.S., Chang, C.C.Y., Khechfe, A.I., Hunter, Y.R., 1996. Implications of dissolved sulfides and organic substances for the chemical speciation of trace contaminants in the water column of San Francisco Bay, California. In: Hollibaugh, J.T. (Ed.), San Francisco Bay: The Ecosystem. American Association for the Advancement of Science, Pacific Division, San Francisco, pp. 157–172.

Kuwabara, J.S., Topping, B.R., Moon, G.E., Husby, P., Lincoff, A., Carter, J.L., Croteau, M.N., 2005. Mercury accumulation by lower trophic-level organisms in lentic systems within the Guadalupe River Watershed, California. US Geological Survey Scientific Investigations Report 2005–5037.

Lahvis, G.P., Wells, R.S., Kuehl, D.W., Stewart, J.L., Rhinehart, H.L., Via, C.S., 1995. Decreased lymphocyte responses in free-ranging bottlenose dolphins (*Tursiops truncatus*) are associated with increased concentrations of PCBs and DDT in peripheral blood. Environ. Health Perspect. 103, 67–72.

Lake, C.A., Lake, J.L., Haebler, R., McKinney, R., Boothman, W.S., Sadove, S.S., 1995. Contaminant levels in harbor seals from the northeastern United States. Arch. Environ. Contam. Toxicol. 29, 128–134.

Landis, W.G., Yu, M.H., 2004. Introduction to Environmental Toxicology: Impacts of Chemicals Upon Ecological Systems. Lewis Publishers, Boca Raton, FL, p. 484.

Landrum, P.F., Robbins, J.A., 1990. Bioavailability of sediment associated contaminants to benthic invertebrates. In: Baudo, R., Giesy, J., Muntau, H. (Eds.), Sediment: Chemistry and Toxicity of In-Place Pollutants. CRC Press, Boca Raton, FL, pp. 237–264.

Larson S.J., Gilliom, R.J., Capel, P.D., 1999. Pesticides in streams of the United States—Initial results from the National Water-Quality Assessment Program, US Geological Survey Water-Resources Investigations Report 98-4222.

Laville, N., Ait-Assima, S., Gomez, F., Casellas, C., Porcher, M., 2004. Effects of human pharmaceuticals on cytotoxicity, EROD activity and ROS production in fish hepatocytes. Toxicology 196, 41–55.

Lee, B.G., Luoma, S.N., 1998. Influence of microalgal biomass on absorption efficiency of Cd, Cr, and Zn by two bivalves from San Francisco Bay. Limnol. Oceanogr. 43, 1455–1466.

Lemly, A.D., 1998. Pathology of selenium poisoning in fish. In: Frankenberger, Jr., W.T., Engberg, R.A. (Eds.), Environmental Chemistry of Selenium. Marcel Dekker, New York, pp. 281–296.

Linville, R.G., Luoma, S.N., Cutter, L., Cutter, G.A., 2002. Increased selenium threat as a result of invasion of the exotic bivalve *Potamocorbula amurensis* into the San Francisco Bay-Delta. Aquat. Toxicol. 57, 51–64.

Long, E.R., Morgan, L.G., 1991. The potential for biological effects of sediment-sorbed contaminants in the national status and trends program. NOAA Technical Memorandum NOS OMA.

Long, E.R., MacDonald, D.D., Smith, S.L., Calder, F.D., 1995. Incidence of adverse biological effects within ranges of chemical concentrations in marine and estuarine sediments. Environ. Manage. 19, 81–97.

Lowe, D.M., Fossato, V.U., DePledge, M.H., 1995. Contaminant-induced lysosomal damage membrane damage in blood cells of mussels *M. galloprovincialis* from the Venice Lagoon: an in vitro study. Mar. Ecol. Prog. Ser. 129, 189–196.

Luengen, A.C., Friedman, C.S., Raimondi, P.T., Flegal, A.R., 2004. Evaluation of mussel immune responses as indicators of contamination in San Francisco Bay. Mar. Environ. Res. 57, 197–212.

Luoma, S.N., 1996. The developing framework of marine ecotoxicology: pollutants as a variable in marine ecosystems. J. Exp. Mar. Biol. Ecol. 200, 29–55.

Luoma, S.N., Ho, Y.B., Bryan, G.W., 1995. Fate, bioavailability and toxicity of silver in estuarine environments. Mar. Pollut. Bull. 31, 44–54.

Luoma, S.N., van Geen, A., Lee, B.G., Cloern, J.E., 1998. Metal uptake by phytoplankton during a bloom in South San Francisco Bay: Implications for metal cycling in estuaries. Limnol. Oceanogr. 43, 1007–1016.

MacArthur, R.H., Connell, J.H., 1966. The Biology of Populations. Wiley, New York, p. 200.

Martineau, D., De Guise, S., Fournier, M., Shugart, L., Girard, C., Lagace, A., Beland, P., 1994. Pathology and toxicology of beluga whales from the St. Lawrence Estuary, Quebec, Canada. Past, present, and future. Sci. Total Environ. 154, 201–215.

Mason, R.P., Reinfelder, J.R., Morel, F.M.M., 1996. Uptake, toxicity and trophic transfer of mercury in a coastal diatom. Environ. Sci. Technol. 30, 1835–1845.

Meng, L., Moyle, P.B., Herbold, B., 1994. Changes in abundance and distribution of native and introduced fishes of Suisun Marsh. Trans. Am. Fish. Soc. 123, 498–507.

Mitra, K., 2003. Histopathology: an effective tool for assessing environmental impact on fish health. In: Methods of Assessment of Aquatic Ecosystem for Fish Health Care. Bulletin du Centre Inland Fisheries Research Institute, Barrackpore, No. 115, pp. 140–142.

Mounho, B.J., Burchiel, S.W., 1998. Alterations in human B cell calcium homeostasis by polycyclic aromatic hydrocarbons: possible associations with cytochrome P450 metabolism and increased protein tyrosine phosphorylation. Toxicol. Appl. Pharmacol. 149, 80–89.

Moyle, P.B., 1994. The decline of anadramous fishes in California. Conserv. Biol. 8, 869–870.

Moyle, P.B., 2002. Inland Fishes of California, second ed. University of California Press, Berkeley, p. 502.

Nakata, H., Kannan, K., Jing, L., Thomas, N., Tanabe, S., Giesy, J.P., 1998. Accumulation pattern of organochlorine pesticides and polychlorinated biphenyls in southern sea otters (*Enhydra lutris nereis*) found stranded along coastal California, USA. Environ. Pollut. 103, 45–53.

Nakata, H., Sakakibara, A., Kanoh, M., Kudo, S., Watanabe, H., Nagai, N., Miyazaki, N., Asano, Y., Tanabe, S., 2002. Evaluation of mitogen-induced responses in marine mammal and human lymphocytes by in-vitro exposure of butyltins and non-ortho coplanar PCBs. Environ. Pollut. 120, 245–253.

Neale, J.C.C., 2004. Persistent organic contaminants and contaminant-induced immune and health alterations in the harbor seal, *Phoca vitulina*. Ph.D. Dissertation, University of California at Davis, p. 147.

Neale, J.C.C., Van de Water, J.A., Harvey, J.T., Tjeerdema, R.S., Gershwin, M.E., 2002. Proliferative responses of harbor seal (*Phoca vitulina*) T lymphocytes to model marine pollutants. Dev. Immunol. 9, 215–221.

Neale, J.C.C., Kenny, T.P., Gershwin, M.E., 2004. Cloning and sequencing of protein kinase cDNA from harbor seal (*Phoca vitulina*) lymphocytes. Clin. Dev. Immunol. 11, 157–163.

Neale, J.C.C., Gulland, F.M.D., Schmelzer, K.R., Harvey, J.T., Berg, E.A., Allen, S.G., Greig, D.J., Grigg, E.K., Tjeerdema, R.S., 2005a. Contaminant loads and hematological correlates in the harbor seal (*Phoca vitulina*) of San Francisco Bay, California. J. Toxicol. Environ. Health 68, 617–633.

Neale, J.C.C., Kenny, T.P., Tjeerdema, R.S., Gershwin, M.E., 2005b. PAH- and PCB-induced alterations of protein tyrosine kinase and cytokine gene transcription in harbor seal (*Phoca vitulina*) PBMC. Clin. Dev. Immunol. 12, 91–97.

Neale, J.C.C., Schmelzer, K.R., Gulland, F.M.D., Berg, E.A., Tjeerdema, R.S., 2005c. Organohalogen levels in harbor seal (*Phoca vitulina*) pups increase with duration of nursing. J. Toxicol. Environ. Health 68, 687–691.

Ning, X., Cloern, J.E., Cole, B.E., 2000. Spatial and temporal variability of picocyanobacteria *Synechococcus* sp. in San Francisco Bay. Limnol. Oceanogr. 45, 695–702.

Ogle, R.S., Gunther, A.J., Hoenicke, R., Bell, D., Cotsifas, J., Gold, J., Salop, P., 2001. Episodic Ambient Water Toxicity in the San Francisco Estuary. Regional Monitoring Program Annual Report. San Francisco Estuary Institute, Oakland, CA.

Ohlendorf, H.M., 1993. Marine birds and trace elements in the temperate North Pacific. In: Vermeer, K., Briggs, K.T., Morgan, K.H., Siegel-Causey, D. (Eds.), The Status, Ecology, and Conservation of Marine Birds of the North Pacific. Canadian Wildlife Service Special Publication, Ottawa, pp. 232–240.

Ohlendorf, H.M., 2003. Ecotoxicology of selenium. In: Hoffman, D.J., Rattner, B.A., Burton, Jr., G.A., Cairns, Jr., J. (Eds.), Handbook of Ecotoxicology, second ed. Lewis Publishers, Boca Raton, FL, pp. 465–500.

Ohlendorf, H.M., Gala, W.R., 2000. Selenium and Chevron Richmond Refinery's water enhancement wetland: a response to A.D. Lemly, 1999. Hum. Ecol. Risk Assess. 6, 903–905.

Ohlendorf, H.M., Marois, K.C., 1990. Organochlorines and selenium in California night-heron and egret eggs. Environ. Monit. Assess. 15, 91–104.

Ohlendorf, H.M., Lowe, R.W., Kelly, P.R., Harvey, T.E., 1986. Selenium and heavy metals in San Francisco Bay diving ducks. J. Wildl. Manage. 50, 64–71.

Ohlendorf, H.M., Custer, T.W., Lowe, R.W., Rigney, M., Cromartie, E., 1988. Organochlorines and mercury in eggs of coastal terns and herons in California, USA. Colonial Waterbirds 11, 85–94.

Ohlendorf, H.M., Marois, K.C., Lowe, R.W., Harvey, T.E., Kelly, P.R., 1991. Trace elements and organochlorines in surf scoters from San Francisco Bay, 1985. Environ. Monit. Assess. 18, 105–122.

Ohlendorf, H.M., Byron, E.R., Santolo, G.M., Tsang, M.A., Gala, W.R., Hegedus, A.S. III., Kinkela, D.F., 2001. Selenium reduction through adaptive management of a treatment wetland. In: The Paper Presented at the Annual Meeting of the Society of Environmental Toxicology and Chemistry, Baltimore, MD (Abstract #526).

Oros, D.R., David, N., 2002. Identification and evaluation of unidentified organic contaminants in the San Francisco Estuary. San Francisco Estuary Institute Contribution 45, Oakland, CA.

Oros, D.R., Ross, J.R., 2004. Polycyclic aromatic hydrocarbons in San Francisco Estuary sediments. Mar. Chem. 86, 169–184.

O'Shea, T.J., 2000. Cause of seal die-off in 1988 is still under debate. Science 290, 1097.

O'Shea, T.J., Brownell, R.L., 1998. California seal lion (*Zalophus californianus*) populations and ΣDDT contamination. Mar. Pollut. Bull. 36, 159–164.

Parchaso, F., Thompson, J.K., 2002. Influence of hydrologic processes on reproduction of the introduced bivalve *Potamocorbula amurensis* in northern San Francisco Bay, California. Pacific Sci. 56, 329–345.

Pearson, T.H., Rosenberg, R., 1978. Macrobenthic succession in relation to organic enrichment and pollution of the marine environment. Oceanogr. Mar. Biol. Annu. Rev. 16, 229–311.

Pennington, P.L., Daugomah, J.W., Colbert, A.S., Fulton, M.H., Key, P.B., Thompson, B.C., Strozier, E.D., Scott, G.I., 2001. Analysis of pesticide runoff from mid-Texas estuaries and risk assessment implications for marine phytoplankton. J. Environ. Sci. Health B 36, 1–14.

Phillips, B.M., Anderson, B.S., Hunt, J.W., Thompson, B., Lowe, S., Hoenicke, R., Tjeerdema, R., 2003. Causes of sediment toxicity to *Mytilus galloprovincialis* in San Francisco Bay, California. Arch. Environ. Contam. Toxicol. 45, 492–497.

Purkerson, D.G., Doblin, M.A., Bollens, S.M., Luoma, S.N., Cutter, G.A., 2003. Selenium in San Francisco Bay zooplankton: Potential effects of hydrodynamics and food web interactions. Estuaries 26, 956–969.

Qian, D., Weiss, A., 1997. T cell antigen receptor signal transduction. Curr. Opin. Cell Biol. 9, 205–212.

Ramalingam, K., 2003. Toxic stress and animal metabolism. Uttar Pradesh J. Zool. 23, 27–34.

Rattner, B.A., Melancon, M.J., Custer, T.W., Hothem, R.L., 1996. Cytochrome P450 and contaminant concentrations in nestling black-crowned night-herons and their interrelation with sibling embryos. Environ. Toxicol. Chem. 15, 715–721.

Ratushnyak, A.A., Andreeva, M.G., Trushin, M.V., 2005. Influence of the pyrethroid insecticides in ultralow doses on the freshwater invertebrates (*Daphnia magna*). Fresenius Environ. Bull. 14, 832–834.

Regan, H.M., Colyvan, M., Burgman, M.A., 2002. A taxonomy and treatment of uncertainty for ecology and conservation biology. Ecol. Appl. 12, 618–628.

Reijnders, P.J.H., 1980. Organochlorine and heavy metal residues in harbour seals from the Wadden Sea and their possible effects on reproduction. Netherlands J. Sea Res. 14, 30–65.

Reijnders, P.J.H., 1986. Reproductive failure in common seals feeding on fish from polluted coastal waters. Nature 324, 456–457.

Rhodes, S., Farwell, A., Hewitt, L.M., MacKinnon, M., Dixon, D.G., 2005. The effects of dimethylated and alkylated polycyclic aromatic hydrocarbons on the embryonic development of Japanese medaka. Ecotoxicol. Environ. Saf. 60, 247–258.

Risebrough, R.W., Alcorn, D., Allen, S.G., Anderlini, V.C., Booren, L., DeLong, R.L., Fancher, L.E., Jones, R.E., McGinnis, S.M., Schmidt, T.T., 1980. Population Biology of Harbor Seals in San Francisco Bay, California, National Technical Information Service, MMC-76/19.

Roepke, T.A., Snyder, M.J., Cherr, G.N., 2005. Estradiol and endocrine disrupting compounds adversely affect development of sea urchin embryos at environmentally relevant concentrations. Aquat. Toxicol. 71, 155–173.

Ross, J.R., Oros, D.R., 2004. Polycyclic aromatic hydrocarbons in the San Francisco Estuary water column: sources, spatial distributions, and temporal trends (1993–2001). Chemosphere 57, 909–920.

Ross, P., De Swart, R., Addison, R., Van Loveren, H., Vos, J., Osterhaus, A., 1996. Contaminant-induced immunotoxicity in harbour seals: wildlife at risk. Toxicology 112, 157–169.

Ross, P.S., Vos, J.G., Birnbaum, L.S., Osterhaus, A.D., 2000. PCBs are a health risk for humans and wildlife. Science 289, 1878–1879.

Schlekat, C.E., Decho, A.W., Chandler, G.T., 2000a. Bioavailability of particle-associated silver, cadmium, and zinc to the estuarine amphipod *Leptocheirus plumulosus* through dietary ingestion. Limnol. Oceanogr. 45, 11–21.

Schlekat, C.E., Dowdle, P.R., Lee, B.G., Luoma, S.N., Oremland, R.S., 2000b. Bioavailability of particle-associated Se to the bivalve *Potamocorbula amurensis*. Environ. Sci. Technol. 34, 4504–4510.

Schlekat, C.E., Lee, B.G., Luoma, S.N., 2002. Assimilation of selenium from phytoplankton by three benthic invertebrates: effect of phytoplankton species. Mar. Ecol. Prog. Ser. 237, 79–85.

Schlekat, C.E., Purkerson, D.G., Luoma, S.N., 2004. Modeling selenium bioaccumulation through arthropod food webs in San Francisco Bay, California, USA. Environ. Toxicol. Chem. 23, 3003–3010.

Schwarzbach, S.E., Adelsbach, T.A., 2003. Assessment of ecological and human health impacts of mercury in the Bay-Delta watershed. Task 3A, field assessment of exposure of aquatic birds to mercury using the avian egg. Final Report to the Calfed Mercury Project, California Bay Delta Authority, Sacramento, CA.

Schwarzbach, S.E., Henderson, J.D., Thomas, C.M., Albertson, J.D., 2001. Organochlorine concentrations and eggshell thickness in failed eggs of the California clapper rail from South San Francisco Bay. Condor 103, 620–624.

Schwarzbach, S.E., Albertson, J.D., Thomas, C.M., 2006. Impacts of predation, flooding and contamination on the reproductive success of the California clapper rail (*Rallus longirostris obsoletus*) in San Francisco Bay. Auk 123, 45–60.

Setzler-Hamilton, E.M., Whipple, J.A., Macfarlane, R.B., 1988. Striped bass populations in Chesapeake and San Francisco Bays, USA: two environmentally impacted estuaries. Mar. Pollut. Bull. 19, 466–477.

She, J., Petreas, M., Winkler, J., Visita, P., McKinney, M., Kopec, D., 2002. PBDEs in the San Francisco Bay area: measurements in harbor seal blubber and human breast adipose tissue. Chemosphere 46, 697–707.

Smital, T., Luckenbach, T., Sauerbrn, R., Hamdoun, A.M., Vega, R.L., Epel, D., 2004. Emerging contaminants—pesticides, PPCPs, microbial degradation products and natural substances as inhibitors of multixenobiotic defense in aquatic organisms. Mutat. Res. 552, 101–117.

Spies, R.B., Rice Jr., D.W., 1988. The effects of organic contaminants on reproduction of starry flounder, *Platichthys stellatus* (Pallas) in San Francisco Bay, Part II: reproductive success of fish captured in San Francisco Bay and spawned in the laboratory. Mar. Biol. 98, 191–202.

Spies, R.B., Rice Jr., D.W., Felton, J.W., 1988. The effects of organic contaminants on reproduction of starry flounder, *Platichthys stellatus* (Pallas) in San Francisco Bay, Part I: hepatic contamination and mixed-function oxidase (MFO) activity during the reproductive season. Mar. Biol. 98, 181–189.

Spies, R.B., Gunther, A.J., Stegeman, J.J., Woodin, B., Smolowitz, R., Saunders, B., Hain, L., 1993. Biomarker induction in *Citharichthys stigmaeus* by contaminated sediments. Am. Zool. 33, 58–65.

Stehr, C.M., Myers, M.S., Burrows, D.G., Krahn, M.M., Meador, J.P., McCain, B.B., Varanasi, U., 1997. Chemical contamination and associated liver diseases in two species of fish from San Francisco Bay and Bodega Bay. Ecotoxicology 6, 35–65.

Stenzel, L.E., Hickey, C.M., Kjelmyr, J.E., Page, G.W., 2002. Abundance and distribution of shorebirds in the San Francisco area. Western Birds 33, 69–98.

Steppan, L., DeKrey, G.K., Fowles, J.R., Kerkvliet, N.I., 1993. Polychlorinated biphenyl (PCB) induced alterations in the cytokine profile in the peritoneal cavity of mice during the course of P815 tumor rejection. J. Immunol. 150, 134A.

Stewart, B.S., Yochem, P.K., 1994. Ecology of harbor seals in the southern California Bight. In: Halverson, W., (Ed.), Proceedings of the Fourth Channel Islands Symposium, Santa Barbara Museum of Natural History, Santa Barbara, CA, p. 20.

Stewart, A.R., Luoma, S.N., Schlekat, C.E., Doblin, M.A., Hieb, K.A., 2004. Food web pathway determines how selenium affects aquatic ecosystems: a San Francisco Bay case study. Environ. Sci. Technol. 38, 4519–4526.

Strong, C.M., Spear, L.B., Ryan, T.P., Dakin, R.E., 2004. Forster's tern, Caspian tern, and California gull colonies in San Francisco Bay: habitat use, numbers and trends, 1982–2003. Waterbirds 27, 411–423.

State Water Resources Control Board (SWRCB), 2006. Development of Sediment Quality Objectives for Enclosed Bays and Estuaries. CEQA Scoping Meeting, Informational Document. State Water Resources Control Board, Division of Water Quality, Sacramento, CA, 75pp.

Tanabe, S., Watanabe, S., Kan, H., Tatsukawa, R., 1988. Capacity and mode of PCB metabolism in small cetaceans. Mar. Mammal Sci. 4, 103–124.

Tanabe, S., Iwata, H., Tatsukawa, R., 1994. Global contamination by persistent organochlorines and their ecotoxicological impact on marine mammals. Sci. Total Environ. 154, 163–177.

Teh, S.J., Clark, S.L., Brown, C.L., Luoma, S.N., Hinton, D.E., 1999. Enzymatic and histopathologic biomarkers as indicators of contaminant exposure and effect in Asian clam (*Potamocorbula amurensis*). Biomarkers 4, 497–509.

Teh, S.W., Deng, D.F., Warner, I., Teh, F.C., Silas, S.O., 2005. Sublethal toxicity of orchard stormwater runoff in Sacramento splittail *Pogonichthys macrolepidotus* larvae. Mar. Environ. Res. 59, 209–213.

Thompson, D.R., 1996. Mercury in birds and terrestrial mammals. In: Beyer, W.N., Heinz, G.H., Redmon-Norwood, A.W. (Eds.), Environmental Contaminants in Wildlife. CRC Press, Boca Raton, FL, pp. 341–356.

Thompson, B., Lowe, S., 2003. Benthic assemblages in the Napa-Sonoma Marsh. In: Schladow, S.G. (Ed.), CISNet San Pablo Bay Network of Environmental Stress Indicators. Report to US EPA, University of Califonia, Davis.

Thompson, B., Lowe, S., 2004. Assessment of macrobenthos response to sediment contamination in the San Francisco Estuary. Environ. Toxicol. Chem. 23, 2178–2187.

Thompson, B., Anderson, B., Hunt, J., Taberski, K., Phillips, B., 1999. Relationships between sediment toxicity and contamination in San Francisco Bay. Mar. Environ. Res. 48, 285–309.

Thompson, B., Lowe, S., Kellogg, M., 2000. Macrobenthic assemblages of the San Francisco Bay-Delta, and their responses to abiotic factors. Regional Monitoring Program Technical Report 39, San Francisco Estuary Institute, Oakland, CA.

Topping, B.R., Kuwabara, J.S., Marvin-DiPasquale, M.C., Agee, J.L, Kieu, L.H., Flanders, J.R., Parchaso, F., Hager, S.W., Lopez, C.B., Krabbenhoft, D.P., 2004. Sediment remobilization of mercury in South San Francisco Bay, California. US Geological Survey Scientific Investigations Report 2004-5196.

Trost, R.E., 2002. Pacific Flyway 2001–2002 Fall and Winter Waterfowl Survey Report. US Fish and Wildlife Service, Office of Migratory Bird Management, Portland, OR.

US EPA, 1998. Water Quality Criteria and Standards Plan–Priorities for the Future. EPA 822-R-98-003. Office of Water, US Environmental Protection Agency, Washington, DC, 54pp.

US EPA, 2005. National Coastal Condition Report II. EPA 620/R-03-002, US Environmental Protection Agency, Washington, DC.

US Fish and Wildlife Service (USFWS), 2002. Waterfowl population status, 2002. US Department of the Interior, Washington, DC, 51pp.

US Geological Survey (USGS), 2005. Access US Geological Survey–San Francisco Bay and Delta. ⟨http://sfbay.wr.usgs.gov/⟩.

Van Loveren, H., Ross, P.S., Osterhaus, A.D.M.E., Vos, J.G., 2000. Contaminant-induced immunosuppression and mass mortalities among harbor seals. Toxicol. Lett. 112–113, 319–324.

Varanasi, U., Stein, J.E., Tilbury, K.L., Meador, J.P., Sloan, C.A., Clark, R.C., Chan, S.L., 1994. Chemical contaminants in gray whales (*Eschrichtius robustus*) stranded along the west coast of North America. Sci. Total Environ. 145, 29–53.

Waalkes, M.P., Perez-Olle, R., 2000. Role of metallothionein in metabolism, transport, and toxicity of metals. In: Koropatnick, D.J., Zalups, R. (Eds.), Molecular Biology and Toxicology of Metals. Taylor & Francis, London.

Wagemann, R., Stewart, R.E.A., Beland, P., Desjardins, C., 1990. Heavy metals and selenium in tissues of beluga whales, *Delphinapterus leucas*, from the Canadian Arctic and the St. Lawrence Estuary. Can. Bull. Fish. Aquat. Sci. 224, 191–206.

Warnock, N., Page, G.W., Ruhlen, M., Nur, N., Takekawa, J.Y., Hanson, J.T., 2002. Management and conservation of San Francisco Bay salt ponds: effects on migrant and wintering Pacific Flyway waterbirds. Waterbirds 25, 79–92.

Weeks, B.A., Huggett, R.J., Warinner, J.E., Mathews, E.S., 1990. Macrophage responses of estuarine fish as bioindicators of toxic contamination. In: McCarthy, J.F., Shugart, L.R. (Eds.), Biomarkers of Environmental Contamination. CRC Press, Boca Raton, FL, pp. 193–204.

Weiss, A., Littman, D.R., 1994. Signal transduction by lymphocyte antigen receptors. Cell 76, 263–274.

Werner, I., Nagel, R., 1997. Stess proteins HSP60 and HSP70 in three species of amphipods exposed to cadmium, diazinon, dieldrin, and fluoranthene. Environ. Toxicol. Chem. 16, 293–2403.

Werner, I., Deanovic, L.A., Connor, V., de Vlaming, V., Bailery, H.C., Hinton, D.E., 2000. Insecticide-caused toxicity to *Ceriodaphnia dubia* (Cladocera) in the Sacramento-San Joaquin River Delta, California, USA. Environ. Toxicol. Chem. 19, 215–227.

Werner, I., The, S.J., Datta, S., XiaoQiao, L., Young, T.M., 2004. Biomarker responses in *Macoma nasuta* (Bivalvia) exposed to sediments from northern San Francisco Bay. Mar. Environ. Res. 58, 299–304.

Weston, D.P., Mayer, L.M., 1998. In vitro digestive fluid extraction as a measure of the bioavailability of sediment associated polycyclic aromatic hydrocarbons: sources of variation and implications for partitioning models. Environ. Toxicol. Chem. 17, 820–829.

Weston, D.P., You, J., Lydy, M.J., 2004. Distribution and toxicity of sediment-associated pesticides in agriculture-dominated water bodies of California's Central Valley. Environ. Sci. Technol. 38, 2752–2759.

Weston, D.P., Holmes, R.W., You, J., Lydy, M.J., 2005. Aquatic toxicity due to residential use of pyrethroid insecticides. Environ. Sci. Technol. 39, 9778–9784.

Whitehead, A., Kuivila, K.M., Orlando, J.L., Kotelevtsev, S., Anderson, S.L., 2004. Genotoxicity in native fish associated with agricultural runoff events. Environ. Toxicol. Chem. 23, 2868–2877.

Wood, T.M., Baptista, A.M., Kuwabara, J.S., Flegal, A.R., 1995. Diagnostic modeling of trace metal partitioning in South San Francisco Bay. Limnol. Oceanogr. 40, 345–358.

Wootton, E.C., Dyrynda, E.A., Pipe, R.K., Ratcliffe, N.A., 2003. Comparisons of PAH-induced immunomodulation in three bivalve mollusks. Aquat. Toxicol. 65, 13–25.

Xu, Y., Wang, W.X., 2004. Silver uptake by a marine diatom and its transfer to the coastal copepod *Acartia spinicauda*. Environ. Toxicol. Chem. 23, 682–690.

Young, D., Becerra, M., Kopec, D., Echols, S., 1998. GC/MS analysis of PCB congeners in blood of the harbor seal *Phoca vitulina* from San Francisco Bay. Chemosphere 37, 711–733.