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Marine Toxins: Adverse Health Effects and Biomonitoring with Resident Coastal Dolphins

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Abstract

Ecotoxicologic studies of marine environments are complex. Expanding knowledge should take into account toxicology, ecology, biology, medicine, and global as well as local anthropogenic disturbances of ecosystems. These areas of interest are discussed, leading to recommendations for biomonitoring of a specific location. Marine mammals are useful as bioindicators of environmental disturbance and as sentinels of health risks for humans who frequently consume seafood. A small community of bottlenose dolphins (*Tursiops truncatus*) in West Galveston Bay, Texas, with strong site fidelity is discussed here for consideration as a local environmental biomonitor. These dolphins are subject to a number of environmental impacts, including industrial toxins, nonpoint source agricultural and residential runoff, and pollutants from vessels. Other threats include climate change and toxic algal blooms. Marine mammal mass mortality events linked to morbillivirus infections in other areas have been associated with one or more of these environmental disturbances. Toxic effects described in cetacean literature generally do not include neurotoxic changes because specific tests for aquatic mammals are not yet available. Neurotoxicity has been addressed in studies of humans who consume contaminated seafood; specific findings are included in this review because marine mammals are likely to be subject to similar adverse effects. Researchers designing biomonitor studies need to keep in mind the multiple and complex impacts caused by both local and global issues. Known impacts on Galveston Bay are outlined and considered in suggesting local biomonitor study designs. Small populations of near-shore resident dolphins can serve more effectively as useful upper trophic level environmental bioindicators with such a multidisciplinary approach.

Key Words: ecotoxicology, seafood, health, bottlenose dolphin, *Tursiops truncatus*, biomonitor, sentinel species, biomarker

Introduction

Anthropogenic contaminants and related disturbances within marine ecosystems have been increasingly recognized in recent years as having related adverse effects on both people and marine mammals, with contaminated seafood as a common denominator. Numerous studies have evaluated the usefulness of marine mammals as bioindicators of environmental disturbance (Berrow et al., 2002; Brenez et al., 2004; Fossi et al., 2003). Dolphins are good candidates as sentinel species for the aquatic health of a local ecosystem (O'Shea et al., 1998) because some dolphin populations preferentially stay in particular areas (Wells et al., 1987; Würsig & Harris, 1990), and they are apex predators occupying a high position in the food web. A small community of common bottlenose dolphins (*Tursiops truncatus*) in West Galveston Bay, Texas, has demonstrated evidence for such site fidelity (Irwin & Würsig, 2004; Maze & Würsig, 1999). In this paper, these animals will be used as an example of resident dolphins with potential as local environmental biomonitors. In addition, pertinent recent literature will be reviewed, providing evidence for human health risks related to seafood consumption, particularly for the very young.

When marine mammals are viewed as indicators of human health risk (Ross, 2000), there may be added benefits for researchers from the perspective of ecotoxicological risk assessment. While recognizing that differences exist in physiological responses to toxins in different species, studies that demonstrate evidence for toxin loads with or without associated toxicity in animals resident to an area where humans harvest seafood remain pertinent to human health concerns. When the benefits of such studies to human health risks are understood by funding agencies, opportunities for research funding tend to expand.

Xenobiotic (chemicals foreign to the biological system) toxicities that have received the bulk of attention in the marine mammal field relate to immunotoxicity and endocrine disturbances

(O'Shea, 1999; Reijnders, 1986; Tanabe et al., 1994). Carcinogenesis, mutagenesis, and teratogenesis (birth defects) also have been considered. Although neurotoxicity is well-known as one of the possible complications of exposure to xenobiotics, this area has not been emphasized in the marine mammal literature because there are few relevant tests that can be applied to wild aquatic mammals. This review will explore some recent advances that contribute to understanding xenobiotic-induced neurotoxicity, particularly in humans, in view of the implications for potential similar effects in marine mammals.

The determination of a clear cause-and-effect relationship of a toxic exposure to a specific pathologic finding is extremely complex. For example, many factors have been thought to play a role in recent marine mammal mass mortality events secondary to morbillivirus, including toxin loads and exposure to harmful algal blooms. In addition, when testing for biomarkers of exposure in biopsy studies, it must be kept in mind that numerous toxins may have the potential to induce these biomarkers. When biomarkers are demonstrated in the study of sentinel species, various known inducers of those markers need to be considered before a relationship to any one agent can be strongly suspected.

As biopsy studies of marine mammals increase with the advent of improved technology, there is a need for further emphasis on study designs that relate to specific questions about local contaminants. This report presents a compilation of pertinent human impacts on the Galveston Bay system where the dolphins studied reside and also briefly reviews global environmental anthropogenic impacts, as they are pertinent to monitoring techniques and benefits in all locations.

This report covers a number of interrelated topics that are all relevant to the development of optimal designs for biomonitoring near-shore ecosystems using resident dolphins as a sentinel species. Maximizing the usefulness of data for the particular locale is especially important when the community of animals under investigation is very small, as biopsies, including skin and some blubber, are the most common tissue harvesting techniques. It is important to minimize risk to the animals and maximize relevant data from small samples. Knowledge of local contaminants, as well as more general knowledge related to findings in other disciplines that might apply, should result in improved efficiency and productivity in these studies.

Adverse Health Effects on Marine Mammals and Humans Due to Consumption of Contaminated Seafood

Over two billion people worldwide rely on seafood as their major source of protein (Knap et al., 2002). Many more consume seafood at significant levels. Sixty percent of the world's human population lives in coastal areas, and that estimated percentage is on the rise (Dewailly et al., 2002). Near-shore dolphins and people eat similar marine foods, so any indication of toxicity or toxin loads in dolphins related to their diet has implications for humans who regularly eat seafood from that same area and vice versa. Dolphins and humans also both represent multi-generational end-point receptors in the process of biomagnification of pollutants through the food chain.

Investigations of seafood consumption and the associated effects on humans have paralleled those in marine mammals. One human example is noted in a study by Bjerregaard et al. (2001), which showed statistically positive correlations of polychlorinated biphenyl (PCB) body burdens in Greenland Inuit in males by age (as females offload their burdens to their children). Their marine diet included consumption of marine mammals as well as fish. The authors were able to determine that bioaccumulation of PCBs began in the 1950s. There was evidence for continued concentration increases over time, despite constant levels of seafood intake.

Dolphins as Environmental Bioindicators or Sentinel Species

Importance of Dolphins as a Sentinel Species

Coastal dolphin populations are subject to many stresses that may play varying roles in their health and behavior. These include anthropogenic pressures that may result in habitat degradation, pollution with various secondary effects, physical injury, noise, loss of food resources, climate change, algal blooms, and diseases (Fair & Becker, 2000). It is important that the basic physiology of a species be reasonably understood when attempting to identify pathological alterations, especially when cause and effect epidemiology is a concern (Tyler et al., 1998). Bottlenose dolphins are particularly attractive as a sentinel species because they have been studied extensively both in captivity and in the wild and more is known about their physiology (Reddy et al., 2001) and behavior than most other marine mammals. Bottlenose dolphins are high trophic-level consumers that carry high fat loads, and some populations show long-term site fidelity. When a resident community of dolphins spends a substantial portion of its time within the confines of a bay, the animals are susceptible to any localized environmental degradation, including toxins (Lynn & Würsig, 2002).

Armstrong et al. (1987) stated that studying an entire ecosystem is not economically feasible. Studies should be designed to emphasize

components of the system that represent "barometers" of environmental events. Coastal dolphins could be one such barometer. One of the most appealing features of studying a small resident community of dolphins is the range of options available for assessing long-term effects on known individual animals (Reijnders et al., 1999a).

Dolphins and the Bioaccumulation of Toxins

Marine mammals living in near-shore waters close to agricultural and industrial activity tend to accumulate higher concentrations of toxins (O'Shea, 1999). In support of the assumption that local contaminants relate to the exposure potential of resident animals, a recent report demonstrated significant geographic sampling variation in organochlorine levels in blubber biopsies from live bottlenose dolphins from different locations along the United States Atlantic coast (Hansen et al., 2004). In addition, available food sources also could alter the likelihood of exposure to specific toxins. Szefer et al. (2002) demonstrated higher cadmium (Cd) levels in harbor porpoises (*Phocoena phocoena*) from Greenland than those from the Baltic Sea, which the investigators believed could be explained in part by the Greenland porpoises' high consumption of squid (which take up Cd) compared to the Baltic Sea porpoises' high fish consumption.

Dolphin Metabolism of Toxins

Dolphins do not metabolize some toxins as efficiently as humans due to differences in specific cytochrome P450 (CYP) enzyme systems (Boon et al., 1997; Fair & Becker, 2000; Tanabe et al., 1987, 1994). CYP enzyme systems are a family of conjugated proteins containing heme that catalyze the biotransformation of xenobiotics (Hong & Yang, 1997) and are central to the phase I oxidative biotransformation of both xenobiotics and some endogenous compounds (McKinney et al., 2004). The P450 monooxygenase enzymes are part of the group of mixed function oxidases (MFOs). The CYP enzyme families are encoded on specific genes, including CYP1A1, CYPIA2, and CYP2B, whose expression may be induced by the presence of specific xenobiotics.

The 209 PCB congeners have been divided into four groups. These groups exemplify the varying capabilities animals have in breaking down different xenobiotics. It is believed that cetaceans have little or no capacity to metabolize PCB groups I and II. The group III congeners are metabolized by CPYIA isozymes and group IV by CPY2B isozymes.

Some toxins may readily bioaccumulate, magnifying their concentrations in these animals (Tanabe, 1988). Bioaccumulation does not necessarily imply bioavailability, as some lipophilic toxins may be temporarily "locked-up" in fat (Tyler et al., 1998). Lack of bioavailability may be one reason that some high toxin loads appear to be better tolerated in dolphins than humans. Toxins may be released, becoming bioavailable during periods of high fat turnover such as illness, reduced availability of food resources, starvation, or lactation.

Mercury and Other Heavy Metals in Dolphins

High heavy metal loads recently were documented in stranded bottlenose dolphins along the Texas coast. Meador et al. (1999) reported higher levels of lead, copper, and zinc in necropsied stranded bottlenose dolphins from Texas than in those from Florida. In another study, few correlations with high heavy metal loads and disease processes were found in stranded Texas dolphins, again suggesting better tolerance than humans (Turnbull, 1998).

Metal regulatory mechanisms may play a role in allowing aquatic mammals to handle those cumulative body burdens (Bennett et al., 2001). The bioactivity of mercury (Hg) can be modified by a number of other micronutrients, including selenium, methionine, cysteine, and vitamin E (Sweet & Zelikoff, 2001). Hg is most commonly bound to selenium, forming granules of insoluble mercury selenide or tiemannite (HgSe) stored in the liver and other organs (Nigro et al., 2002; Turnbull, 1998). In addition, erythrocytes serve as carriers of methylmercury (MeHg), acting as transitory buffers during its conversion from the toxic to a neutralized form (Ancora et al., 2002).

Metallothioneins (MTs) also play a role in detoxifying metals (Das et al., 2002). MT proteins are induced by toxic metals, such as Hg and Cd, as well as physiological cations, and may then sequester them in the form of complexes; however, in dolphins (in contrast to terrestrial mammals), MTs appear to play only a minor role in Hg detoxification, but a major role in detoxifying Cd (Das et al., 2000; Decaltaldo et al., 2004; Gerpe et al., 2002). Cd is another non-essential, potentially toxic metal that can bioaccumulate. Cd is a carcinogen and also can impair renal, hepatic, pulmonary, immune, and endocrine (particularly gonadal) functions (Turnbull, 1998; Waalkes, 2000).

The only current source of the most toxic form of mercury (MeHg) for humans and marine mammals is consumption of seafood. MeHg is the predominant form of Hg in bottlenose dolphins' brains up until about the age of 8 years (Meador et al., 1999). Younger animals are limited in their ability to demethylate MeHg (Turnbull, 1998). This is unfortunate because neurotoxicity from

MeHg is most severe in young animals. On a more positive note, Betti & Negro (1996) demonstrated that bottlenose dolphins' lymphocytes are more resistant to the cytotoxic and genotoxic effects of MeHg than are lymphocytes from rats (*Rattus norvegicus*) and humans. This finding is consistent with other evidence that these animals are more resistant to adverse effects from high body burdens of heavy metals (Turnbull, 1998).

Marcovecchio et al. (1990) suggested that small cetaceans should be particularly useful as biomonitors of environmental heavy metals in view of their apparent relative tolerance to these substances. These animals are able to carry significant metal loads with limited adverse effects, so studying resident live animals can more readily provide useful data on the levels of metals in the marine environment. Such findings could then sound an important alarm because these substances can be considerably more toxic to humans.

Confounding Factors

A number of confounding factors may alter toxin loads and should be considered when a stranded animal comes to necropsy. Toxin concentrations in decomposing specimens may have changed due to various mechanisms, including depletion of lipid reserves with disease or starvation (O'Shea, 1999) or alterations occurring during decomposition (Borrell & Aguilar, 1990; Reijnders et al., 1999a).

When biopsy analyses of organochlorines from St. Lawrence River Estuary beluga whales (*Delphinapterus leucas*) were compared to measurements from stranded animals in that location, the findings suggested that levels found in the stranded belugas may overestimate levels found in the population as a whole, even though the stranded animals studied did not show physical signs of ill health (Hobbs et al., 2003).

Unless individuals within the population are well-known as a result of long-term study, a problem associated with interpreting biopsy toxin results from free-ranging animals can be the lack of information about their age. On the positive side, their geographic location is clearly documented, whereas stranded animals may have originated some distance away from the stranding site (Hobbs et al., 2003).

Females that have had calves have reduced their toxin loads by transferring substantial portions to their calves during pregnancy and lactation (O'Shea, 1999). Although the lipophilic toxins have been emphasized in this process, there is evidence that reproductive transfer can occur for some of the less lipophilic organochlorine toxins (Aguilar et al., 2002). Metallic pollutants also have been shown to pass into bottlenose dolphin milk (Frodello et al., 2002).

Since the heaviest load of toxins will be offloaded from the mother to her firstborn calf, birth recruitment order becomes an important factor in the calf's initial toxin load. In resident adult male killer whales (*Orcinus orca*) from Prince William Sound, organochlorine loads were found to be highest in first-recruited males (Ylitalo et al., 2001). Studies on bottlenose dolphins have shown higher mortality rates for firstborn calves (Wells, 1991), as well as higher miscarriage rates in first pregnancies (Reddy et al., 2001). In view of these potential losses, it is not always possible to determine when a first pregnancy occurs in a wild dolphin. These authors noted that multiple factors may play a role in first-pregnancy and first-born losses, including lack of maternal experience in calf rearing as well as toxin loads.

Dolphin Site Fidelity

In this paper, a small resident community of bottlenose dolphins in the San Luis Pass/Chocolate Bay area in the far western portion of Galveston Bay (Figure 1), as defined by Irwin & Würsig (2004), is used as an example of a credible environmental biomonitor. There are, on average, 35 resident animals found in West Galveston Bay and the adjacent waters in the Gulf of Mexico.

The dolphins in this region have been studied intensively since 1995, with less extensive study in 1990 contributing to the longer-term data (Maze & Würsig, 1999). Individual recognition using photo-identification of dorsal fins is critical to long-term study of dolphin behavior and invaluable in correlating biopsy data gathered in a biomonitoring study. In addition, with long-term study, the age and sex of individuals ultimately can be determined.

Since resident animals are now identified in West Galveston Bay, opportunistic study of known stranded individuals could occur. The Texas Marine Mammal Stranding Network routinely does extensive necropsies of animals found dead (Cowan, 1993, 1995; Cowan & Smith, 1999) and also rehabilitates live stranded animals, which enables blood and tissue samples to be obtained. Pesticide, PCB (Davis, 1993; Salata, 1993; Salata et al., 1995), and heavy metal (Turnbull, 1998) concentrations previously measured in necropsied bottlenose dolphins from the Texas coast are available for comparative purposes.

Dolphin Responses to Environmental Change and Disturbance

Dolphins are flexible in their behavioral strategies (Shane, 1990) and have been documented moving away from areas in probable response to local changes in temperature and food availability (Defran & Weller, 1999; Hansen & Defran,

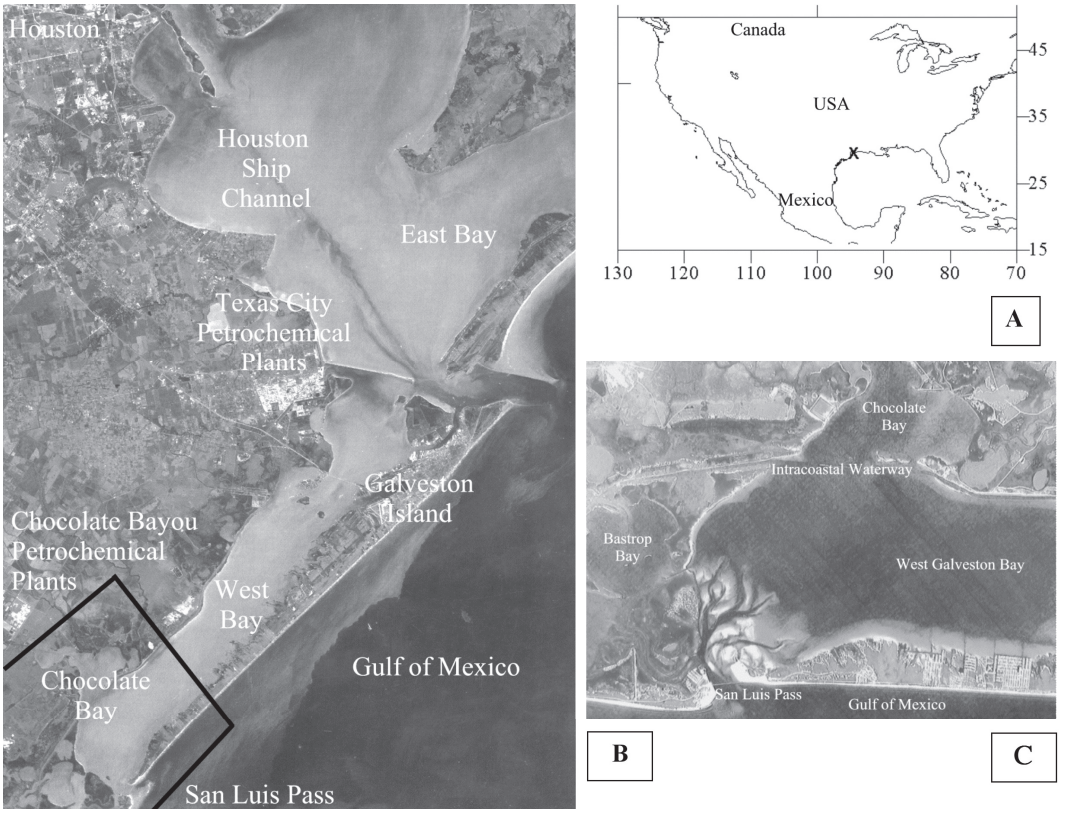

Figure 1. Study site: A. Location on the Texas coast; B. the Galveston Bay Estuary System, with the study area in block; and C. Enlargement of the study site, including far West Galveston Bay, Chocolate Bay, and the nearby Gulf of Mexico

1990; Wells et al., 1990); however, they have been observed to remain in areas with other environmental disturbances, possibly putting themselves at risk. For example, in different instances of significant oil spills in Texas, dolphins were observed swimming, and at times socially interacting, within the spill for long periods (Gruber, 1981; Henningsen & Würsig, 1991; Smultea & Würsig, 1995; Würsig, 1991). During the prolonged red-tide bloom of the toxic algae (*Karenia brevis*) along the Texas Coast from August through October 2000, which involved the West Galveston Bay region, we observed resident dolphins throughout a day in Chocolate Bay (Figure 1), seemingly undisturbed by the noxious fumes and floating dead fish.

It is apparent that dolphins may not leave an area when particular environmentally disastrous events occur, thus making them available as bioindicators for long-term health-related studies relative to such an event. On the other hand, if reduced food availability should occur, their behavioral responses, including possible abandonment of the area, would be another indicator of ecosystem disturbance.

Global Anthropogenic Pollutants and Climate Changes Affecting Marine Environments

Global Pollution

In this paper, the term "toxin" is used as a general term for potentially harmful chemicals, and "toxicant" specifically refers to human-made toxic compounds. When discussing complex mixtures of human-made and natural toxins, the general term "toxin" will apply. The term "anthropogenic contaminants" refers to any substance appearing in nature that would not be there were it not for human activity.

The marine ecosystem has become a repository for anthropogenic contaminants (Minh et al., 2000). One report estimated 2,400 lipophilic and persistent organic pollutants (POPs) in global waters, with 390 of them known toxins with potential for bioaccumulation (O'Shea et al., 1998). Table 1 outlines POPs that are discussed in this paper, including PCBs, polychlorinated dibenzo-p-dixons (PCDDs), dibenzofurans (PCDFs), dichlorodiphenyl trichloroethane (DDT), polycyclic aromatic hydrocarbons (PAHs),

Table 1. Examples of anthropogenic marine toxins discussed in this paper

Toxin type	Abbreviation	Additional information
Dichlorodiphenyl trichloroethane	DDT	Pesticide
Dichlorodiphenyl dichloroethylenes	DDEs	DDT metabolites
Polychlorinated biphyenyls	PCBs	Industrial
Polychlorinated dibenzo-p-dixons	PCDDs	Combustion, including industrial
Dibenzofurans	PCDFs	Combustion, including industrial
Polycyclic aromatic hydrocarbons	PAHs	Incomplete combustion of organic materials
Benzo-a-pyrene epoxides	BaP	PAH metabolites
Polyhalogenated aromatic hydrocarbons	PHAHs	Dioxins and dioxin-like chemicals
2,3,7,8-tetrachlorobenzo-p-dioxin	TCDD	Most toxic PHAH; standard for TEFs
Tributyltin	TBT	Antifoulant paint organotin biocide
Ocotachlorostyrene	OCS	Industrial byproduct
4-hydroxy-heptachlorostyrene	4-OH-HpCS	OCS metabolite
Methylmercury	MeHg	Anthropogenic and natural sources
Persistent organic pollutants	POPs	General term; some with unknown toxicity
Examples of recent concern		
Perfluorochemicals	PFCs	Repel oil and water; resist heat and chemicals
Perfluorooctanic acid	PFOA	Metabolic breakdown product of PFCs
Perfluorooctane sulfonate	PFOS	Metabolic breakdown product of sulfonated PFCs
Polybrominated diphenyl ethers	PBDEs	Flame retardants; added to textiles and others

polyhalogenated aromatic hydrocarbons (PHAHs), tributyltin (TBT), octachlorostyrene (OCS), and MeHg.

Note that the common term "dioxin" refers to a specific group of PHAHs. The toxicity of these structurally related PCBs, PCDDs, and PCDFs is activated by binding with an aryl hydrocarbon receptor (AhR). The resultant dioxin-AhR complex modulates a range of gene transcriptions and expressed proteins. This complex recognizes specific DNA sequences and induces an Ah gene battery to produce the appropriate enzyme and initiate phase 1 of the metabolic process. Some of the resultant metabolites are more potent than their parent compound. For example, hydroxylated PCBs (OH-PCBs) may be more active in disrupting thyroid hormone transport and estrogen receptor binding than their parent PCBs (Brouwer, 1999; Hovander et al., 2002; Li et al., 2003).

Of the various pollutants affecting the marine environment, PCBs and DDT have been the most frequently studied. Although the manufacture of PCBs was banned in most industrialized nations by the 1980s, PCBs that are still in the systems for which they were designed have not yet reached the environment. With degradation, leakage, and disposal, more PCBs will find their way to their ultimate sink, the oceans (Borrell & Reijnders, 1999). Similarly, DDT products, which have been banned in many nations, are still commonly used in some parts of the world (O'Shea, 1999).

In addition to industry, numerous other sources contribute to aquatic pollution, including home and agricultural fertilizer and pesticide runoff, storm sewers, septic systems (including the potential for pharmaceuticals such as synthetic hormones), livestock waste, and illegal dumping by vessels at sea.

Global dispersal of xenobiotics via the atmosphere (Wania & Mackay, 1993) and oceans is now well-recognized, and the ongoing use of these products in any location may result in widespread distribution. Atmospheric transport is particularly efficient for PCBs, and an ongoing temporal shift in global distribution towards the polar regions is anticipated (Aguilar et al., 2002). DDT and its metabolites remain higher in animals in lower latitudes (Tanabe, 2002).

Newly Recognized POPs

Those POPs that have not been studied and whose toxicity is unknown are of equal concern. For example, groups of POPs, which only recently have been evaluated for toxicity, include organic perfluorochemicals (PFCs) and polybrominated diphenyl ethers (PBDEs).

PFCs have been in common use since World War II because of properties that include repelling oil and water, as well as resistance to heat and chemicals. They are in many commercial products for home and personal use, as well as in products used by the aircraft and electronics industries. Perfluorooctane sulfonate (PFOS) is a metabolic breakdown product of several sulfonated fluorochemicals used in coating for textiles as well as in packaging and many other products.

Perfluorooctanic acid (PFOA) is derived from perfluorinated acids used in the manufacture of many products in common use such as Teflon® and Gore-Tex®.

Today, PFOS is found universally in water, fish, humans, and wildlife, including polar bears (*Ursus maritimus*) in northern Alaska (Kannan et al., 2001). PFOS is not only widely distributed; it is extremely stable and is known to accumulate in the blood and liver, rather than in fat. Concerns have been raised about endocrine disruption, carcinogenesis, birth defects, and thyroid dysfunction (Thibodeaux et al., 2003). Yet, because of limited governmental requirements for testing of such products prior to their introduction, their potential for toxicity was not recognized until recently. The U.S. Environmental Protection Agency only began testing in 1999 and subsequently has issued warnings about possible reproductive and cancer risks. The fabric protector, Scotchguard®, is one of the best known sources of PFOS. The 3M company withdrew this product from the market in 2000.

PBDEs have been in widespread use as flame retardants for over 25 years and are found in textiles, upholstery, plastics, electronic equipment, and building materials. Reactive brominated flame retardants (BFRs) are chemically bonded to plastics, but additive BFRs, including PBDEs, are simply mixed into materials and are released more slowly. Some congeners are now ubiquitous in the environment, wildlife, and people. PBDEs are highly lipophilic, environmentally stable, readily bioaccumulate (Alaee & Wenning, 2002), and are structurally similar to PCBs (Tuerk et al., 2005). Recent testing using archived tissues has shown ongoing and significantly increasing concentrations in breast milk of both wildlife and humans (Meironyté et al., 1999). Wildlife examples include harbor seals (She et al., 2002) and beluga whales (LeBeuf et al., 2004). While some PCBs and DDTs show signs of slowly diminishing body burdens, PBDEs are rapidly increasing in the environment. A Swedish study on human breast milk was one of the first to clearly show these trends. The study was well-controlled, and it only used milk from healthy women nursing their first infants. From 1972 to 1997, PBDE levels doubled every five years (Norén & Meironyté, 2000).

Although many food products contain PBDEs, concentrations tend to be highest in fish, and a strong correlation has been demonstrated between PBDE levels in human milk and the consumption of fish and shellfish (Ohta et al., 2002). They are now considered to be one of the potentially dominant contaminants of aquatic biota (Rayne et al., 2004).

Some PBDE congeners are structurally similar to the thyroid hormones triiodothyronine (T3) and thyroxin (T4). This mimicry results in a high affinity for thyroid hormone binding sites and receptors. They also are transported via the atmosphere. Potential areas of toxicity under investigation, likely involving similar mechanisms and interactions with other xenobiotics, include endocrine disruption, carcinogenicity, and neurotoxicity (McDonald, 2002).

There are species-specific differences in the capacity to metabolize PBDEs. Polar bears appear to be particularly efficient and, therefore, are not suitable for monitoring these xenobiotics (Wolkers et al., 2004). PBDEs are not regulated in North America, but regulations are being initiated in Europe (LeBeuf et al., 2004). The European Commission has proposed a new European Union regulatory framework for chemicals called REACH (Registration, Evaluation, and Authorization of Chemicals), which creates incentives for companies to produce safer chemicals.

These scenarios are reminiscent of the long delay between the initial uses of DDT and PCBs and the recognition of their biotoxicity. Recent findings of PFOS and PBDE toxicity may only be "the tip of the iceberg" in view of the lack of testing on so many POPs already on the market.

Climate Change

Global warming, climate change (Harvell et al., 1999), and the changing nature of nutrient loading (Sarokin & Schulkin, 1992) probably have been important contributing factors to many recent events affecting various marine organisms. For example, oceanographic changes are thought to play a role in both the severity and range of harmful algal blooms (HABs) on a global basis (Millie et al., 1999). Some factors thought to relate to altered HAB distribution and behavior include eutrophication, anomalous weather events, global warming, and transport of algae in ships' ballast (van Dolah, 2000).

Toxins and Their Mechanisms of Injury

Toxins may cause injury directly or indirectly. The indirect means may occur with biotransformation of a toxin into a more toxic form, or by creating abnormalities in biological systems that may result in further dysfunction in other biological systems. These issues are further complicated by the possibility that some complex mixtures of toxicants may act synergistically or antagonistically, making their individual effects difficult to test and quantify.

Reproductive Hormonal Disturbances

Reproductive hormonal disturbances affect both sexes and may be categorized as feminizing (which could include estrogenic and/or

anti-androgenic factors) or masculinizing (including anti-estrogenic and/or androgenic effects) (Fossi et al., 2003). For example, some DDT isomers are estrogen mimics, whereas a DDE (a DDT metabolite) is an androgen receptor antagonist (Dewailly et al., 2002). Reduced testosterone levels have been associated with increasing levels of DDE in adult male Dall's porpoises (*Phocoenoides dalli*), which is consistent with such an anti-androgen effect (Tanabe, 2002).

Estrogen receptors are transcription-factor nuclear proteins that modulate gene expression. They are normally activated by binding with the endogenous estrogen receptor ligand (a ligand is a molecule that binds to another molecule). Many xenobiotics and their metabolites may induce various responses that disrupt this system. Different species may have estrogen receptors with different binding affinities for various estrogen-disrupting chemicals that mimic the estrogen receptor ligand (Matthews & Zacharewski, 2000), so different species may respond differently to the same stimulus. This must be taken into account when extrapolating findings in wildlife to humans and vice versa.

Disruptions in Thyroid Physiology

Thyroid hormones are essential in regulating many biological functions, including embryonic and postnatal development. Thyroid function may be altered via several possible mechanisms, including competition for binding sites on transport proteins and membrane carrier systems as well as the disruption of synthesis and secretion of hormones (Skaare et al., 2001). Transthyretin (TTR) is one of the transport proteins for thyroid hormones susceptible to disruption by xenobiotic competition for binding sites. A complex with TTR and retinol-binding protein (RBP) also occurs. Disruption of vitamin A (retinol) transport may then be seen in conjunction with thyroid pathology when the TTR-RBP complex is affected (Braathen et al., 2004). This is presumably a mechanism related to the retinol reductions that have been correlated with high toxin levels and associated thyroid abnormalities (Skaare et. al., 2001).

Biological systems are intricately interrelated, and xenobiotic-induced abnormal physiological responses in one system may lead to changes in other systems. Abnormal thyroid function is a likely contributing factor in the development of a number of xenobiotic-induced neurologic abnormalities.

Direct and Indirect Toxicities

The following limited discussion is presented to provide a small window into the problematic nature of determining the precise adverse effects of a single agent. Examples given here include the direct toxicities of butyltin compounds, particularly tributyltin (TBT), and the indirect toxic effects that arise through biotransformation processes. Endocrine dysfunction related to neurotoxic effects will be discussed in the neurotoxicity section.

Tributyltin (TBT)—TBT has been used extensively as a biocide in antifoulant paints since the late 1960s and is known to leach into water. Its use on vessels under 25 m in length was banned in many countries in the 1980s. Application on ocean-going commercial and military ships initially was felt to be less important because they operated on the open seas. The International Convention on the Control of Harmful Antifoulant Systems recently recommended worldwide phase-out of TBT application by 2003 and removal from all hulls by 2008. TBT is retained in sediments (Ciesielski et al., 2004), and small cetaceans are known to bioaccumulate this material (Iwata et al., 1995). Although there is now evidence for butyltin accumulation in pelagic marine mammals (Law et al., 1999), which indicates widespread oceanic distribution, coastal marine mammals are believed to be at particular risk (Takahashi et al., 2000).

TBT adversely affects both endocrine (Heidrich et al., 2001; Yamabe et al., 2000) and immune systems in animals (LeBlanc & Bain, 1997; Tyler et al., 1998), and there is evidence for neurotoxicity as well (Kishimoto et al., 2001). An example of a severe human organotin-induced neurotoxic event occurred after accidental laboratory exposure to trimethyltin. In addition to the severe acute encephalopathic symptoms, the involved student had persistent seizures, memory loss, and other cognitive changes for years (Feldman et al., 1993). Pathological processes affecting the cerebellar and limbic systems, including the amygdala, have been described in humans in both acute and chronic trimethyltin exposures (Besser et al., 1987).

Concern also has been raised regarding TBT toxicity to humans consuming contaminated fish (Kannan & Falandysz, 1997). In addition to fish contamination from ship hulls, another source of TBT in human diets has been fish farmed from TBT-treated cages. Whalen et al. (1999) found unexpectedly high levels of butyltins in their human subjects. She and colleagues also found evidence that one of the immunotoxic effects of TBT is the inhibition of natural killer (NK) cells (Whalen & Loganathan, 2001), with laboratory evidence that even short-term exposure causes persistent negative effects on NK cells (Whalen et al., 2002). Other studies related to immune dysfunction evaluated TBT as an agent

catalyzing apoptosis (programmed cell death) of lymphocytes (Stridh et al., 2001) and thymocytes (Grundler et al., 2001). Heidrich et al. (2001) found that butyltins inhibit human cytochrome P450 aromatase activity involved in the conversion of androgens to estrogens. There are few studies of mechanisms for TBT neurotoxicity, but Kishimoto et al. (2001) found evidence for altered GABAnergic neurotransmission in mammalian neurons. One of the common mechanisms found in both immunotoxicity and neurotoxicity with TBT is increased intracellular calcium (Kishimoto et al., 2001; Stridh et al., 1999).

Biotransformation Effects—If toxins are metabolized, they may be either deactivated or activated, resulting in different adverse effects (Bearer, 2000). There are many other confounders, such as the enzyme systems of male mammals, that may be more efficient in transforming xenobiotics, causing males to be at higher risk for the effects of toxic metabolites (Aguilar et al., 1999). CYP1A activity, one of the most common biomarkers of effect in current use, is induced by a number of toxins, as detailed in the following section.

There are no simple answers to decoding the metabolic disruption caused by xenobiotics; toxins may act directly or indirectly or by both modes. There are many mechanisms whereby natural metabolic pathways may be altered, including shutting down a pathway or flooding it with non-natural metabolites that are preferentially bound. The more that is learned about the intricate details of these adverse effects, the better positioned researchers will be to track down the specific toxins that cause known effects or patterns of abnormality.

Materials and Methods

Two recent methods chosen for discussion here include (1) a focused system based on the assignment of toxic equivalency factors (TEFs) as a means of approximating the toxic potential of xenobiotics and (2) a broader approach using biomarkers designed to indicate the presence and activity of toxicants in biological systems.

Toxic Equivalency Factors (TEFs)

In 1997, a World Health Organization meeting adopted the use of class-specific TEFs for PCDDs, PCDFs, and PCBs relative to the most potent congener, 2,3,7,8-tetrachlorobenzo-p-dioxin (TCDD) (Van den Berg et al., 1998). These are calculated on the assumption that the toxic effects are additive. While this approach is helpful in assigning relative toxicity values to some toxicants, it is useful only for those non-ortho-substituted coplanar dioxin-like chemicals that bind to the aryl hydrocarbon (Ah) receptor, the "dioxin receptor" (Sahlberg et al., 2002).

Risk assessment using only TEFs may underestimate health risks. For example, it has been shown that ortho-substituted noncoplanar PCB congeners with little or no Ah-receptor activity are responsible for important neurotoxic effects via other mechanisms, as discussed in the "Neurotoxicity" section.

Biomarkers

The biomarker approach differs from TEFs in a fundamental way. Instead of trying to assess the explicit toxicity of each potentially toxic chemical, this approach looks at measurable indicators of responses to toxins.

The study of biomarkers is an active area of research. Some biomarkers may serve as indices of exposure to contaminants prior to the development of obvious pathologic effects, while others may reflect the actual existence of pathological conditions.

There is concern that biomarkers of a "problem" must be clearly linked with the potential cause or causes of that finding, including toxicants as well as other environmental disturbances (McCarty & Munkittrick, 1996). This, of course, is the crux of the complexity of this area of study. At our current stage of knowledge, these markers provide valuable clues and trends, and their value extends beyond single studies and measurements.

Biomarkers in Marine Mammals—Biomarkers of PCB exposures were chosen as one of the first areas for proposed intensive investigation by the International Whaling Commission in their Pollution 2000+ report, which recommended more effective approaches for addressing questions related to the effects of environmental pollutants on cetaceans (Reijnders et al., 1999a). It is important to begin such investigations at the simplest possible level—correlating toxins with measured effects—but it is also necessary to keep in mind that biomarkers generally are not toxin-specific. If apparent biomarkers are discovered, other confounding possibilities must also be investigated.

The use of biomarkers appears to present a more feasible initial monitoring tool than an attempt to quantify the body burden levels of every possible toxicant load, which would be both cumbersome and expensive. Abnormal biomarkers also have the benefit of indicating that there has been a biological effect.

A disadvantage of biomarkers is their general lack of specificity. As has been noted, marine mammals are frequently exposed to complex mixtures of contaminants, some of which may act synergistically or antagonistically, resulting in difficulty establishing clear associations between

contaminant exposure and biological effects (O'Shea, 1999). Further, many new chemicals have unknown toxicity since testing procedures are limited and toxic effects often are discovered only after the product has been sold and used for some time. The added toxicity of metabolites of some parent xenobiotics further complicates the issue.

One advantage of working with the biomarker approach in free-ranging animals is that some of the biomarkers can be studied with skin samples that may be obtained with non-invasive or minimally invasive techniques. Skin is said to be "the largest and most accessible drug-metabolizing organ" (Du et al., 2004). It functions as a barrier to harmful environmental agents and, as such, expresses many P450 cytochromes. At this time, the most common biomarker studies from skin samples relate to CPY1A activity and include the following:

1. High activity of the MFO enzyme benzo (a)pyrene monooxygenase (BPMO) in marine mammal skin biopsies has been associated with high levels of organochlorines (Fossi et al., 1999, 2003, 2004; Marsili et al., 1998).
2. Ethoxyresorufin-O-deethylase (EROD) is also a sensitive indicator of activity of the CYP1A enzyme system and has been correlated with high PCB levels (Tanabe et al., 1994). It is tested by the rate of CYP1A-mediated deethylation of EROD and is used as a correlate for the cumulative presence of dioxin-like toxicants.
3. Immunodetectible CYP1A protein or messenger RNA can be quantified (Hahn, 2002).

An in vitro assay using sperm whale (*Physeter macrocephalus*) skin biopsy material has validated the use of CYP1A expression as a biomarker of chemical exposure in cetaceans (Godard et al., 2004). There are some caveats: If mixtures of xenobiotics contain high concentrations of some PHAHs and PAHs, they may inhibit CYP1A activity, and the resultant assay might not accurately reflect the expected level of induced CYP1A hemoprotein (Hahn, 2002). Note that CYP1A assays, like TEFs, relate only to dioxin-like xenobiotics.

PAH-related benzo(a)pyrene (BaP) DNA adducts also can be measured in skin samples (Peakall, 1999). PAH genotoxicity is a multistage process, with DNA adduct formation an early component which may or may not progress to carcinogenesis (Shaw & Connell, 2001) or mutagenesis (Brouwer, 1999). Pollutant-related DNA alterations include both adduct formation and other changes such as strand breakage (Gauthier et al., 1999).

Newer biomarker techniques under study include batteries of cell culture bioassays (Hahn, 2002), some of which have been proposed for biopsy extract analyses (Hahn, pers. comm.). As an example, CYP1A activity can be induced in cell culture. As test options continue to be added to our armamentarium and the expense of analyses for biomonitoring approaches decreases, the information obtainable with biopsy samples should expand.

If one of the resident dolphins from West Galveston Bay strands or comes to necropsy, correlative testing of both pollutant levels and biomarkers could provide important information not only regarding the status of that individual but also for the design of future testing of apparently healthy resident animals in the wild.

There has been recent interest in epidermal lesions in bottlenose dolphins (Van Bressem et al., 2003; Wilson et al., 2000). PCBs are known to adversely affect Vitamin A, and dermatologic disorders are known to occur with Vitamin A deficiency, as well as with PCB toxicity (Brouwer & Van den Berg, 1986), so visible dermatologic lesions could turn out to be an easily observed biomarker of effect. If these changes are infectious in origin (Van Bressem et al., 1999), they also could relate to an immunocompromised state. Wilson et al. (1999) attempted to correlate the severity and frequency of photographically documented epidermal disease in bottlenose dolphins with published contaminant levels measured in stranded animals from 10 geographic study sites. No such correlation was found, although there was a correlation with regional oceanographic variables. Perhaps that lack of correlation arises from the fact that it was not possible to measure contaminant levels in specific affected individual dolphins. While recognizing that variables, such as salinity and water temperature, appear relevant, further study of known animals with and without epidermal lesions might provide other important correlations. In addition to measuring PCB and other toxin levels, Vitamin A levels also would be pertinent.

Biomarkers in Humans—Biomarkers of the early effects of low-level xenobiotic exposures are also being studied in children. These include EROD activity and DNA adducts in the newborns of Inuit women in arctic Quebec (Lagueux et al., 1999).

Metabolites of toxins also are being addressed because, as noted previously, they may also be toxic. Sandau et al. (2000) examined OH-PCBs, as well as PCBs, in Inuit people from northern Quebec using plasma concentration of omega-3 fatty acids as an indicator of fish intake. The study also measured chlorinated phenolic compounds, most prominently pentachlorophenol (PCP), because of the role that these metabolites also may play in the disruption of thyroid transport mechanisms and

Vitamin A levels. Similarly, in a study of people who consume fatty fish from the Baltic Sea, a correlation was demonstrated between the amount of fish consumed and elevated plasma levels of both PCBs and OH-PCBs (Sjödin et al., 2000).

Biomarkers Summary—It is clear that the job of assessing environmental toxicological impacts is incredibly complex. One of the best possibilities for success in correlating environmental disturbances with the sentinel species' responses may lie in carefully designed longitudinal studies of known individuals within coastal resident dolphin populations. Animals may appear to be healthy at a time when important adverse effects are beginning. Biomarkers will not only be useful long-term monitoring tools, but also may detect evidence for environmental impacts at an early stage, thus directing appropriate research towards the most likely candidate toxins while following trends with repeat testing over time.

Immunotoxicity

Marine Mammals

There has been a great deal of speculation regarding the adverse effects of anthropogenic toxins on marine mammals; however, clear correlations with disease processes have been difficult to establish. One possible exception relates to the question of impaired immunity relative to toxicant loads, such as PCBs and butyltin compounds (Fournier et al., 2000; Lahvis et al., 1995; Ross, 1995), which may make animals more susceptible to infection. Studies of harbor porpoises that died of infection showed higher PCB concentrations in blubber (Jepson et al., 1999) and higher mercury and mercury: selenium ratios in liver (Bennett et al., 2001) than similar animals killed by trauma. Following the immunization of free-ranging polar bears with various mitogens and antigens, Lie et al. (2005) subsequently found correlations between high organochlorine loads and impaired cell mediated immunity. Lahvis et al. (1995) linked reduced T-cell function in wild bottlenose dolphins to high PCB and DDT loads.

Ross's (1995) work with the development of specific immune system dysfunction in harbour seals that were fed contaminated Baltic Sea fish compared to controls correlates with some similar immune system changes found in humans who consume fish from the Baltic Sea (Svensson et al., 1994).

While such findings are highly suggestive of cause-and-effect relationships, they are not definitive since multiple factors could play a role. Inhibition of NK cells, one of the abnormalities found in both seal and human Baltic Sea fish consumption studies, may be induced by various toxicants, including TBT.

Humans: Immune Effects in Children

There is evidence of a higher incidence of infections, suggesting immune dysfunction, in some children exposed to toxins in utero or via their mother's milk (Dewailly et al., 1989, 2000; Reese, 1987). Weisglas-Kuperus et al. (2000) were able to demonstrate not only a higher incidence of middle ear and other infections in young children who had high PCB exposures perinatally but also specific immune parameter changes in the T-cell lymphocyte population that correspond to prenatal exposure. Despite evidence for the transfer of lipophilic toxins in milk, breast feeding was still felt to provide improved immune function in the first few months of life due to maternal antibody transfer and continues to be recommended.

Neurotoxicity

Neurotoxic effects have been evaluated primarily in humans and terrestrial mammals (Mariussen & Fonnum, 2001; Newland & Paletz, 2000; Tilson et al., 1990; Trask & Kosofsky, 2000). Neurological abnormalities have been observed in marine mammals in conjunction with HAB toxicity, as will be noted in the "Mass Mortality Events" section.

Specific neurotoxic effects occur with exposures at defined developmental periods, particularly during the "brain growth spurt" phase in mammals. In rodents, this period spans from neonatal to the first three to four weeks of life. In humans, this critical phase begins in the third trimester of pregnancy and continues at least through the first two years of life. Some of the nervous system features that are rapidly developing during the brain growth spurt include synaptogenesis; dendritic, glial, and axonal growth and proliferation; myelinization of axons; and maximal synthesis of brain lipids allowing significant retention of lipophilic agents (Viberg et al., 2003). Developing neurons are particularly sensitive during this time, as proper temporal and regional sequential processes are crucial (Rice & Barone, 2000). Apoptotic neurodegeneration is one example of an abnormality that can be triggered by very transient toxic exposures (Olney, 2002). In addition to the rapidly evolving brain growth and differentiation in late gestation and the postnatal periods in humans, cytogenesis and histogenesis predominate in the first half of human gestation (Trask & Kosofsky, 2000), so that other developmental abnormalities could be triggered by toxins in this earlier phase.

Single dose exposures of noncoplanar PCBs administered to 10-day old mice (a critical

neurodevelopmental stage) produce permanent abnormal motor behaviors in adult mice (Eriksson, 1997). Mixtures of PCBs can inhibit the uptake of the neurotransmitters dopamine, glutamate, Γ-amino-*n*-butyric acid (GABA), and serotonin (Mariussen & Fonnum, 2001). Neonatal exposure of mice to PCB 52 alters cholinergic receptors in the cerebral cortex, and the adult animals demonstrate learning and memory disorders (Eriksson, 1997). PBDEs also have been shown to induce permanent neurotoxic behavioral effects when neonatal mice are exposed at a specific critical time (Viberg et al., 2003). Three mechanisms are thought be involved: (1) induced thyroid dysfunction, (2) second messenger communication disruption, and (3) neurotransmitter alterations (McDonald, 2002).

Studies of neuropathological mechanisms of the most commonly studied coplanar PCBs with Ah-receptor activity remain in the early stages. One potential important finding comes from Legare et al. (2000) in their recent demonstration of alterations in hippocampal astroglia-neuronal gap junction communication in cell culture. Since the hippocampal structures are important in memory function, this finding may be pertinent to cognitive deficits. Other memory and cognitive-related disturbances may be secondary to neurotransmitter abnormalities caused by specific ortho-substituted noncoplanar PCB congeners with little or no Ah-receptor activity.

Like some PCBs and MeHg, specific brominated flame retardants inhibit uptake of dopamine in synaptic vesicles and nerve terminals in rats (Mariussen & Fonnum, 2003). Noncoplanar PCB-induced abnormalities also include reductions in the neurotransmitter dopamine and alterations in calcium homeostasis (Newland & Paletz, 2000; Tilson & Kodavanti, 1998). Both dopamine synthesis and vesicular uptake may be inhibited. Other neurotransmitters, such as serotonin and norepinephrine, may also be affected, and the mechanisms of effect may differ for acute versus chronic exposure (Mariussen et al., 1999).

Because reduction in the neurotransmitter dopamine is a critical pathological component of Parkinson's Disease, and environmental toxins are thought to be one contributing factor to the development of this disorder, these findings may be relevant in this adult human neurological disorder.

Evidence for cognitive and other neurologic defects in toxin-exposed infants and young children began long before global environmental concerns became widespread. Two severe incidents of PCB toxicity were documented in infants in Japan in the late 1960s and in Taiwan in the late 1970s when mixtures of PCBs and their breakdown products were accidentally introduced into cooking oils. They were both called "oil disease," or Yusho in Japan and Yu-Cheng in Taiwan. Dermatologic, immune, and liver abnormalities predominated in older children and adults (Longnecker et al., 1997). The prenatally exposed Yu-Cheng children continued to demonstrate impaired cognitive development in long-term studies up through the age of 12 (Chen et al., 1992; Lai et al., 2001). Hyperactivity was one of the predominant behavioral problems (Longnecker et al., 1997).

The evaluation of neurotoxic effects associated with seafood is very much in its infancy. There can be many possible interactions and confounders, but the indicators both clinically and in the laboratory show evidence for neurotoxic potential as well as effect (Newland & Paletz, 2000).

One of the early series of studies came from the Lake Michigan population, which examined infants exposed to toxins from mothers whose diets included contaminated Lake Michigan fish (Jacobson & Jacobson, 1996, 1997; Jacobson et al., 1990). They demonstrated deficits in their performance on intelligence quotient (IQ) tests and visual recognition memory testing in the most heavily exposed children, based on PCB levels in maternal blood and milk and in umbilical cord blood. Dose-dependent poor performance relating only to prenatal exposure was documented up to age four, although many of the infants were breast-fed. It appears that in utero exposure is the most significant factor for neurotoxicity in children, with exposure via breast milk being far less important. Lipophilic toxins freely pass the placenta, and the fetus is exposed to the same level of contaminants as the mother (Odland et al., 2003). There is some evidence that breast-fed children are actually less vulnerable to adverse effects of PCB exposure (Jacobson & Jacobson, 2004).

A number of studies on children exposed to xenobiotics in utero report hypotonia (reduced muscle tone) and hyporeflexia (decreased reflexes) in newborns (Longnecker et al., 1997). This subtle finding is far from a definitive abnormality if taken out of context but does give an indication of how difficult it will be to determine whether new generations of children are adversely affected neurologically, even in minor ways, because of such exposures.

The body burden levels of toxins that pose a neurodevelopmental risk in fetuses and infants are not defined clearly. For one well-studied terrestrial toxin, lead, the blood level of medical concern has long been 10 μg per deciliter; however, a recent study has shown that children's IQ scores are inversely associated with lead at concentrations in the 1-10 μg per deciliter range (Canfield et al., 2003). This finding of mild and generally undetected abnormalities even at very low levels

of contamination suggests that there is a tendency to underestimate such risks.

Grandjean et al. (2001) did a prospective study of older children in the Faroe Islands, where marine mammals are consumed, as well as other seafood. When abnormalities on neuropsychological test parameters showed an association with high umbilical cord PCB levels at birth, high cord-blood Hg levels were later demonstrated to be a potential contributing factor. This raises the possibilities of either independent toxicities or interactions between Hg and PCBs. Thus, consideration should be given to similar Hg-PCB interactions or effects in future investigations of seafood-related neurotoxicity since both neurotoxins are common in the marine environment and may simultaneously impact seafood consumers.

An example of another xenobiotic that could be a confounding influence on the results of many studies involving PCBs and MeHg would be the organotin TBT. TBT has adverse effects on the same systems as PCBs and Hg (Kishimoto et al., 2001) and is also a common contaminant in coastal marine environments, yet it is often not considered. Once again, local conditions and local contaminants should be examined to avoid misinterpretation when attempting to correlate toxins and effects. Ongoing studies will help clarify similarities and differences in the biologic effects of specific toxins, both direct and indirect (such as endocrine effects on other systems) (Newland & Paletz, 2000).

Mercury

MeHg is a neurotoxin that may occur in the oceans naturally, as well as anthropogenically. Aquatic methanogenic bacteria rapidly methylate inorganic Hg, subsequently retaining the resultant toxic organic MeHg and serving as the first step in the aquatic food chain for this substance (Clarkston, 1995). MeHg is lipophilic and is biomagnified in the environment (Knap et al., 2002). In recent years, MeHg accumulation in large fatty fish has been a major focus in human health issues related to seafood consumption.

The first known severe human Hg poisoning related to fish consumption occurred in the mid-1950s in Minamata Bay, Japan, and affected 2,500 people. Waste material from a factory using mercuric chloride was discharged directly into the bay. Natural conversion to MeHg occurred, and consumption of contaminated fish ultimately resulted in chronic Hg-related neurotoxicity, which progressed for up to ten years. The offending company and the government did not stop the dumping for several years because it took that long for scientists to show that the inorganic Hg had been methylated in nature. In the meantime, the epidemic spread to people and wildlife in many surrounding areas (Kondo, 2000). Symptoms included loss of balance, sensation, motor function, vision, hearing, and cognition (Rowland, 2000). Initially, prenatally affected children were simply thought to have cerebral palsy because their neurologic involvement was so severe. All of the cases had evidence for mental retardation, loss of balance and coordination, slurred speech, and abnormal postures. Many also had movement disorders, inhibited growth, and other symptoms.

Studies of the affected youngsters in the Minimata Bay event were aided by a particularly helpful local tradition—the drying and preservation of umbilical cords to commemorate births. This made it possible to measure Hg levels long after birth. Results showed that levels remained elevated up to 1970. Although entire families were affected, mothers of the affected children were themselves the least affected, presumably because their Hg loads were transferred to their offspring either trans-placentally (Kondo, 2000) or via lactation. During the time frame of the most severe poisoning, there was also a decrease in male births and a higher proportion of male stillborns, suggesting that male fetuses are more susceptible (Sakamoto et al., 2001).

In an unpublished study, human fish consumption in Texas coastal areas showed a positive association between the number of fish meals eaten per week and blood Hg levels (Alcock et al., 1997). The choice of women as subjects related to the potential for detrimental effects with pregnancy. These findings are pertinent to conditions in Galveston Bay, which was one of the study locations.

In January 2001, the U.S. Food and Drug Administration issued a general warning that pregnant women and women who may become pregnant should not eat certain fish species that may contain Hg levels that could lead to brain damage in a developing fetus. This directive was expanded in 2004. Similar recommendations also were made to limit the consumption of pilot whale (*Globicephalus melas*) meat and blubber by women of child-bearing age in the Faroe Islands. Recently, Hg levels in odontocete meat sold for human consumption in Japan were found to exceed the provisional permitted level set by the Japanese government, suggesting the need for more monitoring of these marketed products (Endo et al., 2003).

MeHg is able to cross the blood-brain barrier by masquerading as the amino acid methionine after forming a methylmercury-cysteine complex (Clarkston, 1995). One of several known neurotoxic effects of MeHg is that of cerebellar dysmorphogensis (developmental malformation)

at particular neurodevelopmental stages, including marked disruption of the cerebellar neuronal elements (Philbert et al., 2000). Considering the importance of motor coordination in marine mammals, such abnormal development of cerebellar structures could produce a devastating handicap. In view of the young animals' limited ability to demethylate Hg (Turnbull, 1998) and the evidence for accumulation of MeHg in their brains (Meador et al., 1999), neurodevelopmental abnormalities may be one area of susceptibility to this toxin.

Examples of Specific Neurodevelopmental Defects

Although the Minimata Bay Hg poisonings and accidental ingestions of PCB-contaminated oils were extreme cases associated with high dose exposures, they provide important evidence for human susceptibility to neurotoxicity from these agents. It will be considerably more difficult to make such definitive associations with low-dose and chronic exposures to toxins that are less likely to be detected or diagnosed, although ongoing insidious effects seem likely in view of essentially 100% detectible levels of common xenobiotics found in human blood samples in the United States (Longnecker et al., 1997).

Brainstem auditory evoked potential abnormalities are one type of objective measurement that has been correlated with neurotoxicity in children. A prolonged I–III interpeak interval has been associated with intrauterine MeHg exposure, as well as some evidence for prolongation of the III–V interpeak interval with later MeHg exposure (Murata et al., 2004). Evoked potential abnormalities have been found with lead toxicity as well.

One class of neurodevelopmental abnormalities that has been associated with toxicant exposures, particularly PCBs, includes attention deficit and hyperactivity disorders in children (ADHD) (Tilson et al., 1990). While this syndrome has become more readily recognized in recent years, it also appears to be more common, raising speculation that this could represent early evidence of toxicants as a factor in altered cerebral function in humans.

Of further interest, cross-species comparisons of adverse developmental effects related to PCB exposure show hyperactivity to be a consistent finding in all species studied (Tilson et al., 1990). Poor performance test results in rhesus monkeys (*Macaca mulatto*) exposed to PCBs were found to be due to attentional deficits and were not believed to be memory related (Newland & Paletz, 2000). The phenobarbital-like noncoplanar PCBs are suspect in this phenomenon. Phenobarbital is also known to trigger hyperactivity in children. Prenatal and lactational exposure to dioxin-like PCBs has not been shown to induce this syndrome (Patandin, 1999).

In addition to their direct neurotoxic effects, PCBs may impact neurological systems by altering thyroid function (Brouwer & Van den Berg, 1986). The resultant thyroid dysfunction may affect neurotransmitters, including dopamine and acetylcholine, particularly in the basal forebrain. The cholinergic system in this area of the brain is one proposed site of pathologic change in ADHD (Porterfield, 2000). Abnormal thyroid function unrelated to toxic exposure has been implicated as one of the factors that may induce hyperactivity, further highlighting the complexity of pinpointing a single cause for a specific effect. Both the toxicant (PCB) and one of its adverse effects therefore might contribute to the ADHD syndrome. Thyroid dysfunction in utero and during the first two years of the life can result in other specific abnormal neurodevelopmental changes, including effects on neuronal proliferation, migration, and differentiation.

Another more devastating neurodevelopmental disorder with a recent alarming increase in incidence is autism. Symptoms range from mild to severe, including defective communication skills and social interaction as well as stereotypical behaviors. Tracking down specific factors that contribute to autistic spectrum disorders (ASD) is proving to be extremely complicated, although xenobiotics are considered to be one likely factor. In view of this possibility, it is notable that there is a preponderance of male cases of ASD. In both ADHD and ASD, there are a number of genetic components that play a role within specific families (Bayes et al., 2005; Serajee et al., 2004). There are also multiple possible environmental inducers for these genes. Edelson & Cantor (1998) found high levels of toxic chemicals as well as abnormal liver detoxification profiles in autistic children. Immune dysfunction has also been shown in children with ASD, with autoimmunity and chronic inflammation described as a component of the cascade of events leading to this disorder (Kidd, 2002). Thus, abnormal liver detoxification would contribute to the higher body burdens of toxins in these children, and the toxins could be having direct effects on the developing nervous system as well as indirect effects via the immune system. In addition to xenobiotics, the autoimmunity may also be triggered by dietary peptides or bacterial toxins (Vojdani et al., 2003), such that causative factors in each case may be unique.

The literature in the field of xenobiotic-induced neurotoxicity is rapidly expanding. Many of the findings in other species may ultimately be found to be useful in future marine mammal and human studies. Hopefully, specific biomarkers of neuropathic effect that may be incorporated into

marine mammal study designs will be among those developments.

As with cetacean studies (Reijnders et al., 1999a), standardization of methods would be helpful in evaluating xenobiotic neurotoxic effects in humans, so that results in different study areas could be compared (Tilson, 2000). Determining exactly which toxins are producing which effect in which developmental time frame will require long-term research.

Other Adverse Human Health Considerations

The ubiquitous nature of lipophilic xenobiotics has resulted in body burdens of these substances throughout the human population. If indeed we are able to clearly demonstrate that low levels of some of these toxins cause subtle (and not-so-subtle) adverse effects on fetuses and infants, particularly those resulting in neurological abnormalities, the development of appropriate environmental monitoring methods should become more urgent.

Other specific human pathological consequences of xenobiotic exposures will not be reviewed in detail in this paper, other than through some brief examples. In an interesting recent human twin study, there was evidence that environmental factors were more significant than genetic predisposition for most cancers (Lichtenstein et al., 2000), increasing concerns about the effects of environmental toxins in carcinogenesis.

Human endocrine studies thus far have evaluated the reproductive systems most extensively. Increasing male reproductive dysfunction may at least in part be related to hormone disrupters. Some specific dysfunctions under study include decreased sperm counts (Rozati et al., 2000) and motility (Richthoff et al., 2003), hypospadias, and testicular cancer (Chevrier et al., 2000). In a consensus statement following the Atlantic Coast Contaminants Workshop in 2000, DeGuise et al. (2001) stated that "the contaminant exposure-endocrine system linkage is no longer a hypothesis, but constitutes a real health hazard to wildlife and humans" (p. 1302). With regard to other areas of toxicity, they emphasized that "lack of data does not mean lack of effects, nor does it mean effects; it just means lack of data" (p. 1302). Deficiencies in our knowledge about xenobiotic-related pathologic processes are most profound in the area of insidious, subtle, and chronic exposures, especially in the very young.

As with the animal studies, the human population is burdened with mixtures of many chemicals, and correlations of specific agents with definitive pathological processes will be a challenge for some time.

Mass Mortality Events and the Complexity of Contributing Factors

Morbilliviruses

Morbilliviruses that have infected cetaceans are newly recognized paramyxoviruses related to measles and distemper (Di Guardo et al., 2005; Kennedy, 1998). Recent epizootics with mass mortality events involving marine mammals have led to speculation about the possible contribution of xenobiotics to the animals' susceptibility to these infections (Aguilar & Borrell, 1994; Aguilar et al., 1999). This subject is addressed here because it serves as an excellent example of potential multifactorial contributions that often need to be considered when looking at environmental cause-and-effect issues.

The earliest evidence for morbillivirus in cetaceans was in the 1980s, although archival sera show morbillivirus antibodies in marine mammals as far back as 1973 (Kennedy, 1998). Recent studies indicate that morbilliviruses have infected cetaceans worldwide (Van Bressem et al., 2001). There are little data regarding symptomatic manifestations in cetaceans, but infected seals have been observed and studied. The clinical findings are similar to those seen in canine distemper, including respiratory distress, hyperthermia, and neurological manifestations (Di Guardo et al., 2005). Central nervous system pathological changes are primarily those of viral encephalitis, and immune system pathology includes generalized lymphoid depletion.

Questions remain about the significance of the toxicant loads that have been demonstrated in some of the animals in morbillivirus-related die-offs (Kuehl et al., 1991; Sarokin & Schulkin, 1992; Watanabe et al., 2000). Although xenobiotic-induced immune deficiency could have been a contributing factor, other influences could have played a similar role. Once an animal is infected with one of these viruses, the virus itself may impair the immune system (O'Shea, 1999), further clouding determination of the cause for laboratory evidence of immunosuppression in necropsied animals.

An alternative explanation for recent morbillivirus epizootics is that some infected animals had not previously been exposed to the virus and, therefore, had simply not yet developed immunity (Kennedy, 1999). In this circumstance, overwhelming infection could occur despite an intact immune system, comparable to deadly epidemics of measles in human populations naïve to this virus (Black, 1966; Donovan, 1969; Herndon, 1996).

It is possible that cetaceans may not maintain a lifelong immunity following infection with morbillivirus as humans do for measles. Morbillivirus

antibodies have been detected in Sarasota Bay, Florida, resident dolphins (although there is no known history of a related mortality event), and antibody titers in some animals have been shown to diminish over time. Since small coastal dolphin populations are not thought to be capable of long-term maintenance of morbillivirus, the antibody responses generated by one exposure to the virus could diminish over time and leave the same population susceptible to another epizootic event years after the last exposure (Duignan et al., 1996).

In 1994, bottlenose dolphin mortalities along the Texas coast were associated with morbillivirus (Krafft et al., 1995; Worthy, 1998). Morbillivirus also may have played a role in the 1992 bottlenose dolphin die-off restricted to Matagorda Bay (Duignan et al., 1996), which lies south of Galveston on the Texas coast. There were unusually heavy winter rains prior to this event, raising speculation that agricultural runoff of pesticides and herbicides was a contributing factor. It is not known whether the West Galveston Bay animals were exposed.

Other considerations of potential importance in the recent occurrence of morbillivirus epizootics include more general global influences, such as changing environmental conditions that may cause increases in the "prevalence and virulence of existing disease or facilitate new diseases" (Harvell et al., 1999, p. 1507), or affect range shifts in either pathogens or their hosts. One such example is that of harmful algal blooms.

Harmful Algal Blooms (HABs)

The toxic algae, *Karenia brevis* (*K. brevis*), (Daugbjerg et al., 2000) (previously called *Gymnodinium breve* or *Ptychodiscus brevis* [Benson et al., 1999]) produce nine brevetoxins (Benson et al., 1999) and may result in Neurotoxic Shellfish Poisoning (NPS). In the case of the 1987-1988 mass mortality event of Atlantic coastal bottlenose dolphins, brevetoxin was found in necropsied animals from that event, causing speculation that the *K. brevis* HAB was the cause of this die-off (Geraci, 1989). The brevetoxin was traced to a 1986-1987 HAB in the Gulf of Mexico (Harwood & Hall, 1990) that may have been transported to the Carolina coasts via the Gulf Stream. While the Carolina bloom occurred later in 1987 than the beginning of the die-off, it was thought that low-level brevetoxin exposure may have occurred during dolphin migrations as the algae moved up the coast (Anderson & White, 1992). Later studies documented evidence that morbillivirus infection was a more probable direct cause of this die-off (Lipscomb et al., 1994).

Brevetoxins have been shown to suppress cell-mediated immunity (Bossart et al., 1998), making exposure a possible indirect factor in dolphin die-offs occurring in association with HAB events. Brevetoxins are sodium channel agonists (Reeves et al., 2001), and they may cause neurotoxicity due to membrane depolarization (van Dolah, 2000) and may also induce teratogenicity (Kimm-Brinson & Ramsdell, 2001). Brevetoxins are distributed systemically both after inhalation (Benson et al., 1999) and consumption of whole fish. They are lipid-soluble and may accumulate in the tissues after repeated exposures, so effects may be acute or chronic and cumulative.

It remains possible that immune dysfunction secondary to sublethal exposure to brevetoxin from such a bloom might have been one of several converging phenomena leading to that particular mass mortality event. In addition to evidence for morbillivirus infection and prior brevetoxin exposure, there was also evidence for high contaminant loads in some animals, and immune system abnormalities were seen at necropsy (Geraci, 1989). Immune dysfunction might have been caused by any or all of these factors, each component likely affecting individual animals to different degrees.

The full complement of adverse effects from HABs on dolphins is not yet clearly defined. The first recorded bottlenose dolphin mass mortality event associated with a massive red tide bloom in the Gulf of Mexico occurred in 1946-1947. More recently, three unusual manatee mortality events have been clearly related to brevetoxin, and two bottlenose dolphin die-offs are suspected to be secondary to brevetoxin exposure. The first dolphin event occurred in 1999-2000; and a briefer event in the spring of 2004 resulted in 107 documented stranding deaths (Anonymous, 2004). In the 1999 case, there was histologic and immunohistochemical evidence that brevetoxins played a role, but the findings were inconclusive (Bossart, pers. comm.). In 2004, high levels of brevetoxins were found at necropsy, and there was no evidence of morbillivirus; further studies are ongoing (Anonymous, 2004).

Including *K. brevis*, approximately 60 species of toxic microalgae have been identified in the marine environment (Pierce & Kirkpatrick, 2001). A diatom HAB genus, *Pseudonitzschia*, produces the glutamate receptor agonist domoic acid which results in Amnestic Shellfish Poisoning (ASP) in humans. The excitotoxic neuronal depolarization triggered by domoic acid results in a cascade of events, including activation of voltage gated calcium channels (Silvagni et al., 2005).

Pseudonitzschia australis blooms are common along the California coast. In the 1998 bloom in Monterey Bay, stranded California sea lions (*Zalophus californianus*) were studied by Scholin et al. (2000). In addition to the mortalities, sick animals exhibited neurological dysfunction,

including seizures, head weaving, ataxia, and depression. Necropsies showed typical brain lesions in the hippocampus, which were similar to those found in fatal human cases of domoic acid encephalopathy that were due to consumption of contaminated mussels from Prince Edward Island in 1987 (Teitelbaum et al., 1990). The human survivors with neurologic sequelae from that event had persistent memory disorders as well as other findings. The memory deficits resembled those found in other conditions with bilateral hippocampal loss. In the California blooms, mussels (*Mytilus edulus*) were found to be unaffected, but anchovy (*Engraulis mordax*), a known prey of the sea lions, were contaminated. The neuropathological findings in the animals affected during three such California events from 1998 to 2000 varied with the duration of the illness, primarily involving limbic structures in the brain (Silvagni et al., 2005).

Concern has been expressed regarding the possibility of exposures to HAB toxins in areas beyond the actual HAB, when marine mammals consume exposed fish that have moved away from the bloom, carrying the toxin in their stomachs (Geraci et al., 1989). This could have been another factor in the 1987-1988 Atlantic bottlenose dolphin mass mortality event.

As the complexity of these issues has become more evident in evaluations of prior marine mammal mass mortality events, studies of any future similar events should be better positioned to take into account the potential contributions of all of these factors, including morbillivirus, HABs, and xenobiotics such as PCBs and other immunosuppressing toxins.

Galveston Bay Environmental Issues

There is increasing recognition of the need to understand local anthropogenic disturbances and pollution sources when attempting to design an optimal study for an environmental indicator species in a particular ecosystem (Marsili, 2000; da Silva et al., 2003). For this reason, a compilation of historic and current human disturbances is presented here that may be pertinent to future study of the small resident bottlenose dolphin community in West Galveston Bay.

Historic and Ongoing Factors

The Galveston Bay system is vast and complex and has limited exchange of water with the Gulf of Mexico. It is surrounded by heavy industry, with a population approaching four million in the five counties surrounding the bay that have tidal waters (Lester & Gonzales, 2002b). The Galveston Bay Estuary System has a long history of human impacts. By the 1970s, over 100 years of pollution helped Galveston Bay become listed as one of the ten most polluted bodies of water in the United States (Armstrong & Ward, 1993). Since that time, notable improvement has occurred, although anthropogenic insults to the bay continue.

Numerous local factors contribute to bay pollution. Up to half of the total chemical production in the United States occurs in the surrounding area, as well as 30% of the U.S. petroleum industry (Ditton et al., 1989; Santschi et al., 2001). Numerous oil and gas wells still operate in or near Galveston Bay. Shipping activity in the Houston and Galveston area is among the highest in the nation. Growing population pressures continue to contribute nonpoint source pollutants. Increasing amounts of impervious land cover, such as concrete, contribute to runoff. More than half of the permitted wastewater discharges in Texas enter Galveston Bay (Morse et al., 1993). Since the 1970s, the flagrant dumping of raw sewage into the bay has decreased (Henson, 1993), but boat discharges, septic tanks, and animal waste continue to pollute, and storm sewers on Galveston Island still run directly into the Bay and Gulf. Factors other than pollution have an impact on the ecosystem as well, such as the excessive harvesting of some marine seafood.

Comprehensive study of the pollutants in the 1,550 km^2 of interconnecting bays within the Galveston Bay Estuary System has not been possible. Eastern components of Galveston Bay have been more heavily impacted by industrial and shipping pollution so that the limited resources available for environmental studies have emphasized that portion of the bay (Armstrong & Ward, 1993; Frank et al., 2001). The location of the resident animals in West Galveston Bay could provide a new tool for an area in need of long-term environmental monitoring.

Direct studies in the western portions of the bay have been limited, but the following studies provide some insight:

- Sediment analysis rated Chocolate Bay the 12th most toxic of 34 sites throughout Galveston Bay (Carr, 1993).
- Sediment Quality Triad (SQT) data suggested that "unmeasured chemicals" (p. 1) or conditions were stressing the system (Carr, 1993).
- PCBs have not been detected in West Galveston Bay (Lester & Gonzales, 2002a).
- An increasing trend for DDT and its metabolites has been shown in bottom deposits in West Galveston Bay from the 1980s through 2001, although the levels remain lower than in other areas of the bay (Lester & Gonzales, 2002b).
- Hg and Cd have both been documented in fish and crabs from West Galveston Bay in reports from the Texas Department of Health.

- Within the past 40 years, 95% of sea grasses, which had been found primarily in West Galveston Bay, have been lost (Lester & Gonzales, 2002b; Sheridan et al., 1989), although planting programs have restored some grasses since 1995.
- There have been large-scale losses of marsh and wetland areas critical to juvenile aquatic organisms.

Local Pollutants

Although there is no documented history of serious toxic spill events in Chocolate Bay, where the resident dolphins spend much of their time in warm months, it is a location where negative anthropogenic impacts could occur. Chemical plants operating along Chocolate Bayou deal primarily with petroleum products used in the manufacture of many synthetics. There is heavy barge traffic traversing Chocolate Bay both along the Intracoastal Waterway (ICW) and through the bay to the chemical plants. There are sludge pits adjacent to the ICW, which receive the bulk of their material from paper and petrochemical companies (Armstrong & Ward, 1993).

Agricultural and ranch land lies on the northeast boundary of the area, raising concern about pesticide, herbicide, and animal waste runoff. There is a 440 km^2 watershed area for Chocolate Bayou, over half of which is agricultural (Newell et al., 1992). The increasing trend in concentrations of DDT and DDE in West Galveston Bay in recent years is an unexpected finding in view of the long-standing DDT ban in the United States. Of note, Gulf of Mexico waters likely receive DDT from Mexico, where DDT is currently used for mosquito control (Struntz et al., 2004).

The Environmental Protection Agency Toxics Release Inventory Data 2000 indicates high air emissions of Hg in Texas, primarily from chemical, electric generation, and refuse industries. Over 98% of rain samples in Texas exceeded the EPA human health standard for Hg.

OCS – An Example of an Infrequently Monitored Local Contaminant

Octachlorostyrene (OCS) is one important example of an anthropogenic contaminant found in the Galveston Bay system that is not regularly monitored. OCS is a lipophilic, semivolatile potential mutagen with a high bioaccumulation factor. Concern began in the Galveston area when higher residues of OCS were found in Galveston Bay egret (*Ardea alba*) and heron (*Nycticorax nycticorax*) egg and tissue samples than in eggs and tissues from known highly contaminated locations (Rice & Custer, 1991). This resulted in OCS becoming defined as a site-specific problem in Galveston Bay.

OCS is a byproduct of electrolysis industries. Possible sources of OCS in the Galveston Bay area are industries working with the production of magnesium (Tarkpea et al., 1985) and chlorine (Vogelgesang et al., 1986). OCS is created as a waste product of electrolytic chlorine production using graphite electrodes. Newer methods of chlorine production that do not produce OCS have been available since 1970 (Kaminsky & Hites, 1984), so, ultimately, OCS may diminish in the environment if this is a primary source. No trend data are available in Galveston Bay at this time.

OCS is a known inducer of EROD (Smith et al., 1994) and therefore needs to be considered when EROD or CYP1A are elevated in biomarker studies in this area. Rats exposed to OCS demonstrate a dose-dependent accumulation in fat and liver as well as histological changes in thyroid, liver, and kidney (Chu et al., 1986). There is also an active metabolite, 4-OH-heptachlorostyrene (4-OH-HpCS), which has been found in fish (Li et al., 2003), ringed seals (*Phoca hispida*), polar bears (Sandau et al., 2000), and people (Hovander et al., 2002). This metabolite has been shown to have estrogenic effects (Li et al., 2003) and, like OH-PCBs with similar structures, 4-OH-HpCS has a high binding affinity for the thyroid transport protein TTR (Sandau et al., 2000).

One of the early human studies in Germany found a correlation between fish consumption and OCS levels in people where OCS was a known local pollutant (Lommel et al., 1992). Sandau et al. (2002) included 4-OH-HpCS in their umbilical cord plasma measurements of xenobiotics from different regions of coastal Quebec. They found 4-OH-HpCS in all umbilical cord plasma samples from coastal areas as well as the general population, raising concern about possible thyroid dysfunction and neurodevelopmental effects on the newborns.

Few environmental studies in Texas have tested for OCS contamination, although high OCS concentrations were found in all dolphins tested from Matagorda Bay, Texas, whereas none were found in dolphins from Alabama or Atlantic United States coastal locations (Kuehl & Haebler, 1995).

Recently, OCS and 4-OH-HpCS have been included more commonly in studies done elsewhere (Sandau et al., 2002). Since OCS is an identified local toxicant and has been found in dolphins in nearby Matagorda Bay, it is a logical parameter to include in future dolphin biomonitoring study plans in Galveston Bay.

Continuing Anthropogenic Pressures

Despite overall improvements in the Galveston Bay Estuary System, anthropogenic pressures

are increasing in West Galveston Bay and its surrounding areas. There has been a rapid growth of Galveston West End housing with associated nonpoint-source polluting runoff, as well as increased use of the bay for recreational fishing and boating. Commercial shrimpers are also active in this area, which brings into play TBT, used locally in anti-foulant paints (McFarlane et al., 1989) until it was outlawed for small boats in 1989 because of its extreme biotoxicity. This material is probably still present on some barges, as well as remaining on many smaller boats, as evidenced by recent high TBT levels in oysters from the nearby Houston Yacht Basin (Wade et al., 2001).

The ICW supports heavy industrial barge traffic, which includes chemical products transported to and from the petrochemical plants operating along Chocolate Bayou. In addition to possible pollution from TBT or toxic spill events, passing barges may stir up sediment toxins, as may shrimp trawling and dredging in the ICW and the deep channel running through Chocolate Bay.

Although there is both historical and ongoing concern about the state of Galveston Bay, significant improvement has occurred. Many stakeholders, including government, education, industry, boaters, fishermen, environmental organizations, and the public are now concerned about and involved in bay issues.

West Galveston Bay Dolphins as Sentinel Study Animals – Recommendations

Longitudinal studies related to the health and behavior of the West Galveston Bay dolphins should complement the work of many others who are striving to evaluate and improve the state of the Galveston Bay system. Because this community of animals is very small, careful planning will be necessary to devise a monitoring method that is both safe and locally pertinent. Not only could such studies provide important information about the state of the bay and the safety of seafood for human consumption, they also would relate to the health of the dolphins themselves, as they should be considered valuable natural resources in their own right.

These dolphins are most consistently found within the confines of the bay in summer months, so this would be the logical time to locate them for study; however, this is also the period when recreational fishing is most common in this region. When invasive biopsies are initiated, recreational boaters, fishermen, shrimpers, and other parties who might observe this procedure should be informed and educated about the safety and intent of the study. The potential relevance of the findings to seafood safety for human consumption may be best understood by these parties. The long-term nature of data processing and interpretation must also be addressed. Baseline studies will be imperative for future trend data.

At this time, a biopsy study of this community of dolphins is in the planning stage (H. Petersen, pers. comm.). The use of a recently described, minimally invasive dart-biopsy system devised for small cetaceans (Krützen et al., 2002) is planned. Genetic testing and identification of the animal's gender will not only help to better define the resident animals but can then be used to confirm individual animals resampled at a later date, looking for trends.

In addition to genetic data, biopsy samples can allow some biomarker and/or toxicological data processing. Blubber used for toxicant testing should be deeper than the superficial connective tissue-laden level (Reeves et al., 2001). It is not yet clear how all of the various toxicants might be stratified within the blubber layers as Hobbs et al. (2003) found a great deal of variability between individual animals in this regard. Pending the size of the biopsy obtained, there may be adequate blubber available for toxicology and/or sufficient skin for biomarker studies such as BPMO activity, BaP-DNA adducts, other DNA alterations, metal analysis (Fossi et al., 2003), and/or CYP1A (Fossi et al., 2003; Reeves et al., 2001).

When taking local contaminants into account for study designs for toxin or biomarker detection in the West Galveston Bay resident dolphins, OCS, TBT, and DDT should be considered. In addition, since the chemical plants located along Chocolate Bayou deal primarily with petroleum products, DNA adducts may also be important as biomarkers

Metals are generally not lipophilic (except for MeHg), so that concentrations in blubber are significantly lower than in other tissues such as liver and kidney. Roditi-Elasar et al. (2003) found total Hg levels in skin, blubber, and brain to be in similar ranges in bottlenose dolphins, however. Cd levels in skin tended to be slightly higher than in blubber and brain. Such studies are providing data that may allow estimation of levels in other tissues based on findings in skin and blubber samples. These two toxic metals should be the primary ones considered for testing in this area, based on available prior environmental data. Cd exposure would be less likely if the resident dolphins do not consume significant amounts of squid (Decataldo et al., 2004).

Although lipophilic toxicants are found in cetaceans even in areas removed from heavy human pollution (Tanabe et al., 1994), the degree and composition of bioaccumulated toxins in these

animals should still be significant indicators of local conditions and food sources (Krahn et al., 1999; Ross et al., 2000; Watanabe et al., 2000). The more widespread pollutants and/or their associated biomarkers should be incorporated in the study design if biopsy sample size allows.

Many pollutant and biomarker studies are available for comparative purposes and may be used when attempting to determine the potential significance of the findings from the West Galveston Bay dolphin biopsy study. As noted, biomarkers tend to be nonspecific. They provide a tool, and results must be interpreted in light of the toxins most likely to be present in the study area. Because CYP1A may be influenced by many xenobiotics, including some PCBs, PAHs, and OCS, if elevated CYP1A activity is found, it will be important to devise protocols to evaluate and pursue possible local xenobiotic inducers of this enzyme system. In addition to looking for sources of the problem, further study of seafood in the area as well as people who are heavy seafood consumers may need to be considered.

While the resident animals in West Galveston Bay are being more clearly characterized, other researchers are studying the dolphins seen in the eastern portion of Galveston Bay, which has been more heavily impacted by anthropogenic influences. As individual dolphins are identified as residents in that location, studies designed to compare parameters such as biomarkers of effect and toxin loads in these animals and the West Galveston Bay residents should be considered. It is possible that a gradient of exposure to different toxicants may be demonstrable (Reijnders et al., 1999b).

Long-term data covering significant changes in behavioral patterns could provide valuable information about environmental conditions should significant changes occur. Combining ongoing studies of population dynamics and behavior of sentinel bioindicator organisms with searches for biomarkers of toxic effects may enable researchers to discover changes that provide early warnings if critical environmental disturbances occur. More serious long-term ecotoxicologic consequences may be avoided if this leads to the discovery of the ultimate cause or causes of observed adverse effects.

Conclusions

Regional marine monitoring programs using sentinel species face numerous challenges in determining the relevance of their findings to the local marine ecology (Segar & Stamman, 1986). Carefully designed, long-term monitoring of individual animals in order to seek new findings or trends is a particularly valuable approach. It will always be necessary to recognize that any marine environment, most particularly coastal waters near human population centers, will have complicated mixtures of toxins, some of which may be disproportionately represented in specific regions. With our incomplete knowledge of unknown POPs and their toxicities, new toxicant information also must be factored into our databases in future, and the potential significance of measured biomarkers may need to be reevaluated or expanded.

The West Galveston Bay dolphins are relatively isolated from the larger coastal dolphin population when they are in West Galveston Bay and Chocolate Bay. These resident animals present an opportunity for cooperative studies between disciplines and institutions. We are fortunate to have such a community of dolphins in an area with numerous well-established universities and medical schools in Galveston and nearby Houston. Collaboration of marine mammalogists, medical researchers, veterinarians, ecotoxicologists, oceanographers, industry, environmental managers, and other stakeholders could provide new insight from multiple disciplines and areas of interest that might apply to the study of this population of animals. Keeping abreast of findings in different fields may provide researchers with new perspectives and ideas relevant to their particular area of interest. Interdisciplinary communication is particularly important in environmental studies, as varying effects of toxins on different species need to be compared and considered. Within the confines of our closed global ecosystem, all biological systems may be at various levels of risk considering the number of both known and unknown POPs in our environment.

Working together, it should be possible to determine the most appropriate parameters to study over the long term to optimize information about this location. Study designs are rapidly evolving in many related fields, and useful biomarker information discovered in humans as well as terrestrial and laboratory animals should be considered for testing in other species, including marine mammals. It is important to remain aware of research regarding the implications of ecosystem changes to human health as well.

The realities of funding and politics suggest that investigation and subsequent correction of anthropogenic environmental impacts tend to be more likely when data suggests that the human population is at risk. As evidence mounts that even small doses of some of the environmental toxins found in seafood can be detrimental, particularly to human fetuses and very young children, this argument will continue to gain credibility. If conditions such as hyperactivity-attention

deficit disorder and autism continue to show ongoing increases in frequency, now that diagnostic criteria are more clearly established, questions about environmental toxins' contribution to these and other neurodevelopmental conditions must be answered. Biomonitoring of ecosystems that humans use heavily to harvest seafood should not wait, however, as even the possibility of such toxicities has devastating implications.

While being hopeful that the local environmental indicators will remain positive, it is prudent to look for early warnings of adverse changes in West Galveston Bay and to document baseline data. An opportunity exists to provide information that may contribute to the preservation of this portion of the bay and to protect people as well as dolphins that are eating seafood from this area. There is also the chance to use this well-studied system and its upper-trophic level marine mammal inhabitants as models of ecosystem monitoring that—with appropriate caution—may be extrapolated to other locations around the world.

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Bibliography

Adams, S. M., Giesy, J. P., Tremblay, L. A., & Eason, C. T. (2001). The use of biomarkers in ecological risk assessment: Recommendations from the Christchurch conference on biomarkers in ecotoxicology. *Biomarkers*, *6*, 1-6.

Aguilar, A., & Borrell, A. (1994). Abnormally high polychlorinated biphenyl levels in striped dolphins (*Stenella coeruleoalba*) affected by the 1990-1992 Mediterranean epizootic. *Science of the Total Environment*, *154*, 237-247.

Aguilar, A., Borrell, A., & Pastor, T. (1999). Biological factors affecting variability of persistent pollutant levels in cetaceans. *Journal of Cetacean Research and Management*, (Special Issue 1), 83-116.

Aguilar, A., Borrell, A., & Reijnders, P. J. H. (2002). Geographical and temporal variation in levels of organochlorine contaminants in marine mammals. *Marine Environmental Research*, *53*, 425-452.

Alaee, M., & Wenning, R. J. (2002). The significance of brominated flame retardants in the environment: Current understanding, issues and challenges. *Chemosphere*, *46*, 579-582.

Alcock, N. W., Lederman, R., Wilson, D., Vela-Perez, T., & Ramanujam, V. M. S. (1997). *Potential mercury exposure through diet in pregnant women and women of childbearing age.* Paper 2351 presented to Experimental Biology 97 Conference.

Ancora, S., Rossi, R., Di Simplicio, P., Lusini, L., & Leonzio, C. (2002). In vitro study of methylmercury in blood of bottlenose dolphins (*Tursiops truncatus*). *Archives of Environmental Contamination and Toxicology*, *42*(3), 348-353.

Anderson, D. M., & White, A. W. (1992). Marine biotoxins at the top of the food chain. *Oceanus*, *35*, 55-61.

Anonymous. (2004). *Interim report on the bottlenose dolphin* (Tursiops truncatus) *unusual mortality event along the panhandle of Florida March-April 2004.* Washington, DC: National Oceanic and Atmospheric Administration (NOAA). Available online: www.nmfs.noaa.gov/pr/readinggrm/mmhealth/ume_report_final_061604.pdf.

Armstrong, N. E., Brody, M., & Funicelli, N. (1987). The ecology of open-bay bottoms of Texas: A community profile. In *Biological report* (85-7.12). Washington, DC: U.S. Department of the Interior, Fish and Wildlife Service, Research and Development, National Wetlands Research Center. 104 pp.

Armstrong, N. E., & Ward, G. H., Jr. (1993). *Point source loading characterization of Galveston Bay* (Galveston Bay National Estuary Program publication GBNEP-36). Webster, TX: Galveston Bay National Estuary Program. 198 pp.

Bayes, M., Ramos, J. A., Cormand, B., Hervas-Zuniga, A., Del Campo, M., Duran-Tauleria, E., Ribases, M., Vilella-Cuadrada, E., de Diego-Otero, Y., Casas-Brugue, M., & Estivill, X. (2005). Large-scale genotyping in research into autism spectrum disorders and attention deficit hyperactivity disorder. *Revista de Neurologica*, *40*(Supp. 1), 187-190.

Bearer, C. F. (2000). The special and unique vulnerability of children to environmental hazards. *Neurotoxicology*, *21*, 925-934.

Bennett, P. M., Jepson, P. D., Law, R. J., Jones, B. R., Kuiken, T., Baker, J. R., Rogan, E., & Kirkwood, J. K. (2001). Exposure to heavy metals and infectious disease mortality in harbour porpoises from England and Wales. *Environmental Pollution*, *112*, 33-40.

Benson, J. M., Tischler, D. L., & Baden, D. C. (1999). Uptake, tissue distribution, and excretion of brevitoxin 3 administered to rats by intrathecal instillation. *Journal of Toxicology and Environmental Health*, *Part A*, *56*, 345-355.

Berrow, S. D., McHugh, B., Glynn, D., McGovern, E., Parsons, K. M., Baird, R. W., & Hooker, S. K. (2002). Organochlorine concentrations in resident bottlenose

dolphins (*Tursiops truncatus*) in the Shannon estuary, Ireland. *Marine Pollution Bulletin*, *44*, 1296-1313.

Besser, R., Kramer, G., Thumler, R., Bohl, J., Gutmann, L., & Hopf, H. C. (1987). Acute trimethyltin limbic-cerebellar syndrome. *Neurology*, *37*, 945-950.

Betti, C., & Negro, M. (1996). The Comet assay for the evaluation of the genetic hazard of pollutants in cetaceans: Preliminary results on the genotoxic effects of methyl-mercury on the bottle-nosed dolphin (*Tursiops truncatus*) lymphocytes in vitro. *Marine Pollution Bulletin*, *32*, 545-548.

Bigsby, R., Chapin, R. E., Daston, G. P., Davis, B. J., Gorski, J., Gray, L. E., Howdeshell, K. L., Zoeller, R. T., & vom Saal, F. S. (1999). Evaluating the effects of endocrine disrupters on endocrine functioning during development. *Environmental Health Perspectives*, *107* (Supp. 4), 613-618.

Bjerregaard, P., Dewailly, E., Ayotte, P., Pars, T., Ferron, L., & Mulvad, G. (2001). Exposure of Inuit in Greenland to organochlorines through the marine diet. *Journal of Toxicology and Environmental Health*, *Part A*, *62*, 69-81.

Black, F. L. (1966). Measles endemicity in insular populations: Critical community size and its evolutionary implications. *Journal of Theoretical Biology*, *11*, 207-211.

Boon, J. P., van der Meer, J., Allchin, C. R., Law, R. J., Klungsøyr, J., Leonards, P. E. G., Spliid, H., Storr-Hansen, E., McKenzie, C., & Wells, D. E. (1997). Concentration-dependent changes of PCB patterns in fish-eating mammals: Structural evidence for induction of cytochrome P450. *Archives of Environmental Contamination and Toxicology*, *33*, 298-311.

Borrell, A., & Aguilar, A. (1990). Loss of organochlorine compounds in the tissues of a decomposing stranded dolphin. *Bulletin of Environmental Contamination and Toxicology*, *45*, 46-53.

Borrell, A., & Reijnders, P. (1999). Summary of temporal trends in pollutant levels observed in marine mammals. *Journal of Cetacean Research and Management*, (Special Issue 1), 149-155.

Bossart, G. D., Baden, D. G., Ewing, R. Y., Roberts, B., & Wright, S. D. (1998). Brevetoxicosis in manatees (*Trichechus manatus latirostris*) from the 1996 epizootic: Gross, histologic and immunohistochemical features. *Toxicologic Pathology*, *26*, 276-282.

Braathen, M., Derocher, A. E., Wiig, Ø., Sermo, E. G., Lie, E., Skaare, J. U., & Jenssen, B. M. (2004). Relationships between PCBs and thyroid hormones and retinol in female and male polar bears. *Environmental Health Perspectives*, *112*, 826-833.

Brenez, C., Gerkens, P., Mazzucchelli, G., Jauniauz, T., Eppe, G., De Pauw, E., & De Pauw-Gillet, M-C. (2004). A strategy to identify specific biomarkers related to the effects of a PCDD/F mixture on the immune system of marine mammals. *Talanta*, *63*, 1225-1230.

Brouwer, A. (1999). Induction of biotransformation enzymes by polyhalogenated aromatic hydrocarbons (PAHs): Potential impact on animal physiology and health. *Journal of Cetacean Research and Management*, (Special Issue 1), 209-221.

Brouwer, A., & Van den Berg, K. J. (1986). Transthyretin (prealbumin) binding of PCBs: A model for the mechanism of interference with vitamin A and thyroid hormone metabolism. *Chemosphere*, *15*, 1699-1706.

Canfield, R. L., Henderson, C. R., Cory-Slechta, D. A., Cox, C., Jusko, T. A., & Lanphear, B. P. (2003). Intellectual impairment in children with blood lead concentrations below 10 microgram per deciliter. *New England Journal of Medicine, 348*(16), 1517-1526.

Carr, R. S. (1993). Sediment quality assessment survey of the Galveston Bay system (Galveston Bay National Estuary Program publication GBNEP-30). Webster, TX: Galveston Bay National Estuary Program. 101 pp.

Chen, Y-C. J., Guo, Y-L., Hsu, C-C., & Rogan, W. J. (1992). Cognitive development of Yu-Cheng ("oil-disease") children prenatally exposed to heat-degraded PCBs. *Journal of the American Medical Association*, *268*, 3213-3218.

Chevrier, J., Dewailly, E., Ayotte, P., Mauriège, P., Després, J-P., & Tremblay, A. (2000). Body weight loss increases plasma and adipose tissue concentrations of potentially toxic pollutants in obese individuals. *International Journal of Obesity*, *24*, 1272-1278.

Chu, I., Villeneuve, D. C., Secours, V. E., Valli, V. E., Leeson, S., & Shen, S. Y. (1986). Long-term toxicity of octachlorostyrene in the rat. *Fundamental and Applied Toxicology*, *6*, 69-77.

Ciesielski, T., Wasik, A., Kuklik, I., Skóra, K., Namienik, J., & Szefer, P. (2004). Organotin compounds in the liver tissue of marine mammals from the Polish coast of the Baltic Sea. *Environmental Science and Technology*, *38*, 1415-1420.

Clarkston, T. W. (1995). Environmental contaminants in the food chain. *American Journal of Clinical Nutrition*, *61*(Supp.), 682s-686s.

Cowan, D. F. (1993). Lobo's disease in a bottlenose dolphin (*Tursiops truncatus*) from Matagorda Bay, Texas. *Journal of Wildlife Diseases*, *29*, 488-489.

Cowan, D. F. (1995). Amyloidosis in the bottlenose dolphin, *Tursiops truncatus*. *Veterinary Pathology*, *32*, 311-314.

Cowan, D. F., & Smith, T. L. (1999). Morphology of the lymphoid organs of the bottlenose dolphin, *Tursiops truncatus*. *Journal of Anatomy*, *194*, 505-517.

da Silva, A. M. F., Lemes, V. R. R., Barretto, H. H. C., Oliveira, E. S., de Alleluia, I. B., & Paumgartten, F. J. R. (2003). Polychlorinated biphenyls and organochlorine pesticides in edible fish species and dolphins from Guanabara Bay, Rio de Janeiro, Brazil. *Bulletin of Environmental Contamination and Toxicology*, *70*, 1151-1157.

Das, K., Debacker, V., & Bouquegneau, J. M. (2000). Metallothioneins in marine mammals. *Cellular and Molecular Biology*, *46*, 283-294.

Das, K., Jacob, V., & Bouquegneau, J. M. (2002). White-sided dolphin metalloproteins: Purification, characterization

and potential role. *Comparative Biochemistry and Physiology*, *131C*, 245-251.

Daugbjerg, N., Hansen, G., Larsen, J., & Moestrup, Ø. (2000). Phylogeny of some major genera of dinoflagellates based on ultrastucture and partial LSU rDNA sequence date, including the erection of three new genera of unarmoured dinoflagellates. *Phycologia*, *39*, 302-317.

Davis, J. W. (1993). *An analysis of tissues for total PCB and planar PCB concentrations in marine mammals stranded along the Gulf of Mexico.* M.Sc. thesis, Texas A&M University, College Station, TX. 134 pp.

Decataldo, A., Di Leo, A., Giandomenico, S., & Cardellicchio, N. (2004). Association of metals (mercury, cadmium and zinc) with metallothionein-like proteins in storage organs of stranded dolphins from the Mediterranean sea (Southern Italy). *Journal of Environmental Monitoring*, *6*, 361-367.

Defran, R. H., & Weller, D. W. (1999). Occurrence, distribution, site fidelity, and school size of bottlenose dolphins (*Tursiops truncatus*) off San Diego, California. *Marine Mammal Science*, *15*, 366-380.

DeGuise, S., Shaw, S. D., Barclay, J. S., Brock, J., Brower, A., Dewailly, E., Fair, P. A., Fournier, M., Grandjean, P., Guillette, L. J., Jr., Hahn, M., Koopman-Esseboom, C., Letcher, R. J., Matz, A., Norstrom, R. J., Perkins, C. R., Schwacke, L., Skaare, J. U., Sowles, J., St. Aubin, D. J., Stegeman, J., & Whaley, J. E. (2001). Consensus statement: Atlantic Coast Contaminants Workshop 2000. *Environmental Health Perspectives*, *109*, 1301-1302.

Dewailly, E., Nantel, A., Weber, J. P., & Meyer, F. (1989). High levels of PCBs in breast milk of Inuit women from Arctic Quebec. *Bulletin of Environmental contamination and Toxicology*, *43*, 641-646.

Dewailly, E., Ayotte, P., Bruneau, S., Gingras, S., Belles-Isles, M., & Roy, R. (2000). Susceptibility to infections and immune status in Inuit infants exposed to organochlorines. *Environmental Health Perspectives*, *108*, 205-211.

Dewailly, E., Ayotte, P., Bruneau, S., Laliberté, C., Muir, D. C. G., & Norstrom, R. J. (1993). Inuit exposure to organochlorines through the aquatic food chain in Arctic Quebec. *Environmental Health Perspectives*, *101*, 618-620.

Dewailly, E., Nantel, A., Bruneau, C., Laliberté, C., Ferron, L., & Gingras, S. (1992). Breast milk contamination by PCDDs, PCDFs, and PCBs in arctic Quebec: A preliminary assessment. *Chemosphere*, 25, 1245-1249.

Dewailly, E., Ryan, J. J., Laliberté, C., Bruneau, S., Weber, J. P., Gingras, S., & Carrier, G. (1994). Exposure of remote maritime populations to coplanar PCBs. *Environmental Health Perspectives*, *102*(Supp. 1), 205-209.

Dewailly, E., Furgal, C., Knap, A., Galvin, J., Baden, D., Bowen, B., Depledge, J. M., Duguay, L., Fleming, L., Ford, T., Moser, F., Owen, R., Suk, W. A., & Unluata, U. (2002). Indicators of ocean and human health. *Canadian Journal of Public Health*, *93*(Supp. 1), S34-38.

Di Guardo, G., Marruchella, G., Agrimi, U., & Kennedy, S. (2005). Morbillivirus infections in aquatic mammals: A brief overview. *Journal of Veterinary Medicine, A*, *52*, 88-93.

Ditton, R. B., Loomis, D. K., Fesenmaier, D. R., Osborn, M. O., Hollin, D., & Kolb, J. W. (1989). Galveston Bay and the surrounding area: Human uses, production and economic values. In T. E. Whitledge & S. M. Ray (Eds.), *Galveston Bay: Issues, resources, status, and management* (NOAA Estuary-of-the-Month Seminar Series No. 13). Washington, DC: NOAA. 114 pp.

Donovan, J. W. (1969). A study in New Zealand mortality: 6. Epidemic diseases. *New Zealand Medical Journal*, *70*, 406-415.

Du, L., Hoffman, S. M. G., & Keeney, D. S. (2004). Epidermal CYP2 family cytochromes P450. *Toxicology and Applied Pharmacology*, *195*, 278-287.

Duignan, P. J., House, C., ODell, D. K., Wells, R. S., Hansen, L. J., Walsh, M. T., St. Aubin, D. K., Rima, B. K., & Geraci, J. R. (1996). Morbillivirus infection in bottlenose dolphins: Evidence for recurrent epizootics in the western Atlantic and Gulf of Mexico. *Marine Mammal Science*, *12*, 499-515.

Edelson, S. B., & Cantor, D. S. (1998). Autism: Xenobiotic influences. *Toxicology and Industrial Health*, *14*(4), 553-563.

Endo, T., Hotta, Y., Haraguchi, K., & Sakata, M. (2003). Mercury contamination in the red meat of whales and dolphins marketed for human consumption in Japan. *Environmental Science and Technology*, *37*, 2681-2686.

Eriksson, P. (1997). Developmental neurotoxicity of environmental agents in the neonate. *Neurotoxicology*, *18*, 719-726.

Fair, P. A., & Becker, P. R. (2000). Review of stress in marine mammals. *Journal of Aquatic Ecosystem Stress and Recovery*, *7*, 335-354.

Feldman, R. G., White, R. F., & Eriator, I. I. (1993). Trimethlytin encephalopathy. *Archives of Neurology*, *50*, 1320-1324.

Fossi, M. C., Casini, S., & Marsili, L. (1999). Nondestructive biomarkers of exposure to endocrine disrupting chemicals in endangered species of wildlife. *Chemosphere*, *39*, 1273-1285.

Fossi, M. C., Marsili, L., Neri, G., Natoli, A., Politi, E., & Panigada, S. (2003). The use of a non-lethal tool for evaluating toxicological hazard of organochlorine contaminants in Mediterranean cetaceans: New data 10 years after the first paper published in MPB. *Marine Pollution Bulletin*, *46*, 972-982.

Fossi, M. C., Marsili, L., Lauriano, G., Fortuna, C., Canese, S., Ancora, S., Leonzio, C., Romeo, T., Merino, R., Abad, E., & Jiménez, B. (2004). Assessment of toxicological status of a SW Mediterranean segment population of striped dolphin (*Stenella coeruleoalba*) using skin biopsy. *Marine Environmental Research*, *58*, 269-274.

Fournier, M., Dégas, V., Colborn, T., Omara, F. O., Denizeau, F., Potworowski, E. F., & Brousseau, P.

(2000). Immunosuppression in mice fed on diets containing beluga whale blubber from the St. Lawrence estuary and the Arctic populations. *Toxicology Letters*, *112-113*, 311-317.

Frank, D. S., Mora, M. A., Sericano, J. L., Blankenship, A. L., Kannan, K., & Giesy, J. P. (2001). Persistent organochlorine pollutants in eggs of colonial waterbirds from Galveston Bay and East Texas, USA. *Environmental Toxicology and Chemistry*, *20*, 608-617.

Frodello, J. P., Viale, D., & Marchand, B. (2002). Metal concentrations in the milk and tissues of a nursing *Tursiops truncatus* female. *Marine Pollution Bulletin*, *44*, 551-576.

Gauthier, J. M., Dubeau, H., Rassart, É., Jarman, W. M., & Wells, R. S. (1999). Biomarkers of DNA damage in marine mammals. *Mutation Research*, *444*, 427-439.

Geraci, J. R. (1989). *Clinical investigation of the 1987-88 mass mortality of bottlenose dolphins along the U.S. central and south Atlantic coast* (Final report to the National Marine Fisheries Service and the U.S. Navy, Office of Naval Research and Marine Mammal Commission). Guelph, Ontario: Wildlife Disease Section, Department of Pathology, Ontario Veterinary College, University of Guelph.

Geraci, J. R., Anerson, D. M., Timperi, R. J., St. Aubin, D. J., Early, G. A., Prescott, J. H., & Mayo, C. A. (1989). Humpback whales (*Megaptera novaeangliae*) fatally poisoned by dinoflagellate toxin. *Canadian Journal of Fishes and Aquatic Sciences*, *46*, 1895-1898.

Gerpe, M. S., Rodriquez, D. H., Moreno, V. J., Bastida, R. O., & deMoreno, J. A. E. (2002). Accumulation of heavy metals in the franciscana (*Pontoporia blainvillei*) from Buenos Aires province, Argentina. *The Latin American Journal of Aquatic Mammals*, *1*(Special Issue 1), 95-106.

Goddard, C. A. J., Smolowitz, R. M., Wilson, J. Y., Payne, R. S., & Stegeman, J. J. (2004). Induction of cetacean cytochrome P4501A1 by β-naphthoflavone exposure of skin biopsy slices. *Toxicological Sciences*, *80*, 268-275.

Grandjean, P., Weihe, P., Burse, V. W., Needham, L. L., Storr-Hansen, E., Heinzow, B., Debes, F., Murata, K., Simonsen, H., Ellefsen, P., Budtz-Jørgensen, E., Keiding, N., & White, R. F. (2001). Neurobehavioral deficits associated with PCB in 7-year-old children prenatally exposed to seafood neurotoxicants. *Neurotoxicology and Teratololgy*, *23*, 305-317.

Gruber, J. A. (1981). *Ecology of the Atlantic bottlenosed dolphin* (Tursiops truncatus) *in the Pass Cavallo area of Matagorda Bay, Texas.* M.Sc. thesis, Texas A&M University, College Station, TX. 182 pp.

Grundler, W., Dirscherl, P., Beisker, W., Marx, K., Stampfl, A., Maier, K., Zimmerman, I., & Nüsse, M. (2001). Early functional apoptotic responses of thymocytes induced by tri-n-butyltin. *Cytometry*, *44*, 45-56.

Hahn, M. E. (2002). Biomarkers and bioassays for detecting dioxin-like compounds in the marine environment. *Science of the Total Environment*, *289*, 49-69.

Hansen, L. J., & Defran, R. H. (1990). A comparison of photo-identification studies of California coastal bottlenose dolphins. *Reports of the International Whaling Commission,* (Special Issue 12), 101-104.

Hansen, L. J., Schwacke, L. H., Mitchum, G. B., Hohn, A. A., Wells, R. S., Zolman, E. S., & Fair, P. A. (2004). Geographic variation in polychlorinated biphenyl and organochlorine pesticide concentrations in the blubber of bottlenose dolphins from the US Atlantic coast. *Science of the Total Environment*, *319*, 147-172.

Harvell, C. D., Kim, K., Burkholder, J. M., Colwell, R. R., Epstein, P. R., Grimes, D. J., Hofmann, E. E., Lipp, E. K., Osterhaus, A. D. M. E., Overstreet, R. M., Porter, J. W., Smith, G., & Vasta, G. R. (1999). Emerging marine diseases: Climate links and anthropogenic factors. *Science*, *285*, 1505-1510.

Harwood, J., & Hall, A. (1990). Mass mortality in marine mammals: Its implications for population dynamics and genetics. *Trends in Ecology and Evolution*, *5*, 254-257.

Heidrich, D. D., Steckelbroeck, S., & Klingmuller, D. (2001). Inhibition of human cytochrome P450 aromatase activity by butyltins. *Steroids*, *55*, 763-769.

Henningsen, T., & Würsig, B. (1991). Bottle-nosed dolphins in Galveston Bay, Texas: Numbers and activities. In P. G. H. Evans (Ed.), *European research on cetaceans. Volume 5: Proceedings of the fifth annual conference of the European Cetacean Society.* Sandefjord, Norway, and Cambridge, England.

Henson, M. S. (1993). *The history of Galveston Bay resource utilization* (Galveston Bay National Estuary Program publication GBNEP-39). Webster, TX: Galveston Bay National Estuary Program. 71 pp.

Herndon, R. M. (1996). Evasion of immunological defenses and emerging viral threats. *Archives of Neurology*, *53*, 23-27.

Hobbs, K. E., Muir, D. C. G., Michaud, R., Béland, P., Letcher, R. J., & Norstrom, R. J. (2003). PCBs and organochlorine pesticides in blubber biopsies from free-ranging St. Lawrence River Estuary beluga whales (*Delphinapterus leucas*), 1994-1998. *Environmental Pollution*, *122*, 291-302.

Hong, Y-J., & Yang, C. S. (1997). Genetic polymorphism of cytochrome P450 as a biomarker of susceptibility to environmental toxicity. *Environmental Health Perspectives*, *105*(Supp. 4), 759-762.

Hovander, L., Malmberg, T., Athanasiadou, M., Athanassiadis, I., Rahm, S., Bergman, A., & Wehler, E. K. (2002). Identification of hydroxylated PBC metabolites and other phenolic halogenated pollutants in human blood plasma. *Archives of Environmental Contamination and Toxicology*, *42*, 105-117.

Humphrey, H. E. B. (1987). The human population—An ultimate receptor for aquatic contamination. *Hydrobiologica*, *149*, 75-80.

Irwin, L. J., & Würsig, B. (2004). A small resident community of bottlenose dolphins, *Tursiops truncatus,* in Texas: Monitoring recommendations. *Gulf of Mexico Science*, *22*, 13-21.

Iwata, H., Tanabe, S., Mizuno, T., & Tatsukawa, R. (1995). High accumulation of toxic butyltins in marine mammals from Japanese coastal waters. *Environmental Science and Technology*, *29*, 2959-2962.

Jacobson, J. L., & Jacobson, S. W. (1996). Intellectual impairment in children exposed to polychlorinated biphenyls in utero. *New England Journal of Medicine*, *335*, 783-789.

Jacobson, J. L., & Jacobson, S. W. (1997). Evidence for PCBs as neurodevelopmental toxicants in humans. *Neurotoxicology*, *18*(2), 415-424.

Jacobson, J. L., & Jacobson, S. W. (2004). Prenatal exposure to polychlorinated biphenyls and attention at school age. *Obstetrical and Gynecological Survey*, *59*, 412-413.

Jacobson, J. L., Jacobson, S. W., & Humphrey, H. E. B. (1990). Effects of in utero exposure to polychlorinated biphenyls and related contaminants on cognitive functioning in young children. *Journal of Pediatrics*, *116*, 38-45.

Jepson, P. D., Bennett, P. M., Allchin, C. R., Law, T. K., Baker, J. R., Rogan, E., & Kirkwood, J. K. (1999). Investigating potential associations between chronic exposure to polychlorinated biphenyls and infectious disease mortality in harbour porpoises from England and Wales. *Science of the Total Environment*, *234/244*, 339-348.

Kaminsky, R., & Hites, R. A. (1984). Octachlorostyrene in Lake Ontario: Sources and fates. *Environmental Science and Technology*, *18*, 275-279.

Kannan, K., & Falandysz, J. (1997). Butyltin residues in sediment, fish, fish-eating birds, harbour porpoise, and human tissues from the Polish coast of the Baltic Sea. *Marine Pollution Bulletin*, *34*, 203-207.

Kannan, K., Koistinen, J., Beckmen, K., Evans, T., Gorzelany, J. F., Hansen, K. J., Jones, P. D., Helle, E., Nyman, M., & Giesy, J. P. (2001). Accumulation of perfluorooctane sulfonate in marine mammals. *Environmental Science and Technology*, *35*, 1593-1598.

Kennedy, S. (1998). Morbillivirus infections in aquatic mammals. *Journal of Comparative Pathology*, *119*, 201-225.

Kennedy, S. (1999). Morbilliviral infections in marine mammals. *Journal of Cetacean Research and Management*, (Special Issue 1), 267-273.

Kidd, P. M. (2002). Autism, an extreme challenge to integrative medicine. Part 1: The knowledge base. *Alternative Medicine Review*, *7*(4), 292-316.

Kimm-Brinson, K. L., & Ramsdell, J. S. (2001). The red tide toxin, brevitoxin, induces embryo toxicity and developmental abnormalities. *Environmental Health Perspectives*, *109*, 377-381.

Kishimoto, K., Matsuo, S., Kanemoto, Y., Ishibashi, H., Oyama, Y., & Akaike, N. (2001). Nanomolar concentrations of tri-n-butyltin facilitate γ-aminobotyric acidergic synaptic transmission in rat hypothalamic neurons. *Journal of Pharmacology and Experimental Therapeutics*, *299*(1), 171-177.

Knap, A., Dewailly, E., Furgal, C., Galvin, J., Bowen, R. E., Depledge, M., Duguay, L., Fleming, L. E., Ford, T., Moser, F., Owen, R., Suk, W. A., & Unluata, U. (2002). Indicators of ocean health and human health: Developing a research and monitoring framework. *Environmental Health Perspectives*, *10*, 839-845.

Kondo, K. (2000). Congenital Minamata disease: Warnings from Japan's experience. *Journal of Child Neurology*, *15*, 458-464.

Krafft, A., Lichy, J. H., Lipscomb, T. P., Klaunberg, B. A., Kennedy, S., & Taubenberger, K. (1995). Postmortem diagnosis of morbillivirus infection in bottlenose dolphins (*Tursiops truncatus*) in the Atlantic and Gulf of Mexico epizootics by polymerase chain reaction-based assay. *Journal of Wildlife Diseases*, *31*, 410-415.

Krahn, M. M., Burrows, D. G., Stein, J. E., Becker, P. R., Schantz, M. M., Muir, D. C. G., O'Hara, T. M., & Rowles, T. (1999). White whales (*Delphinapterus leucas*) from three Alaskan stocks: Concentrations and patterns of persistent organochlorine contaminants in blubber. *Journal of Cetacean Research and Management*, *1*, 239-249.

Krützen, M., Barré, L. M., Möller, L. M., Heithaus, M. R., Simms, C., & Sherwin, W. B. (2002). A biopsy system for small cetaceans: Darting success and wound healing in *Tursiops* spp. *Marine Mammal Science*, *18*, 863-878.

Kuehl, D. W., & Haebler, R. (1995). Organochlorine, organobromine, metal, and selenium residues in bottlenose dolphins (*Tursiops truncatus*) collected during an unusual mortality event in the Gulf of Mexico, 1990. *Archives of Environmental Contamination and Toxicology*, *28*, 494-499.

Kuehl, D. W., Haebler, R., & Potter, C. (1991). Chemical residues in dolphins from the U.S. Atlantic coast including Atlantic bottlenose obtained during the 1987/88 mass mortality. *Chemosphere*, *22*, 1071-1080.

Lagueux, J., Pereg, D., Ayotte, P., Dewailly, E., & Poirier, G. G. (1999). Cytochrome P450 CYP1A1 enzyme activity and DNA adducts in placenta of women environmentally exposed to organochlorines. *Environmental Research*, *80*, 369-382.

Lahvis, G. P., Well, 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. *Environmental Health Perspectives*, *103* (Supp. 4), 67-72.

Lai, T. J., Guo, Y. L., Guo, N. W., & Hsu, C. C. (2001). Effect of prenatal exposure to polychlorinated biphenyls on cognitive development in children: A longitudinal study in Taiwan. *British Journal of Psychiatry*, *178* (Supp. 40), s49-s52.

Law, R. J., Blake, S. J., & Spurrier, C. J. H. (1999). Butyltin compounds in liver tissues of pelagic cetaceans stranded on the coasts of England and Wales. *Marine Pollution Bulletin*, *38*, 1258-1261.

LeBeuf, M., Gouteux, G., Measures, L., & Trottier, S. (2004). Levels and temporal trends (1988-1999) of polybrominated diphenyl ethers in beluga whales (*Delphinapterus leucas*) from the St. Lawrence Estuary, Canada. *Environmental Science and Technology*, *38*, 2971-2977.

LeBlanc, G. A., & Bain, L. J. (1997). Chronic toxicity of environmental contaminants: Sentinels and biomarkers. *Environmental Health Perspectives*, *105*(Supp. 1), 65-80.

Legare, M. E., Hanneman, W. H., Barhoumi, R., Burghardt, R. C., & Tiffany-Castiglioni, E. (2000). 2,3,7,8-tetrachlorobenzo-p-dioxin alters hippocampal astroglia-neuronal gap junction communication. *Neurotoxicology*, *21*, 1109-1116.

Lester, J., & Gonzales, L. (Eds.). (2002a). The state of the Bay: A characterization of the Galveston Bay ecosystem (GBEP T-7, AS-186/02). 162 pp. Available online: http://gbic.tamug.edu/SOBDoc/SOB2page.html.

Lester, J., & Gonzales, L. (2002b). *Status and trends database maintenance project final report.* Houston: Environmental Institute of Houston, University of Houston-Clear Lake. 160 pp.

Li, H., Drouillard, K. G., Bennett, E., Haffner, G. D., & Letcher, R. J. (2003). Plasma-associated halogenated phenolic contaminants in benthic and pelagic fish species from the Detroit River. *Environmental Science and Technology*, *37*, 832-839.

Lichtenstein, P., Holm, N. V., Verkasalo, P. K., Iliadou, A., Kaprio, J., Koskenvuo, M., Pukkala, E., Skytthe, A., & Hemminki, K. (2000). Environmental and heritable factors in the causation of cancer. *New England Journal of Medicine*, *343*, 78-85.

Lie, E., Larsen, H. J. S., Larsen, S., Johansen, G. M., Derocher, A. E., Lunn, N. J., Norstrom, R. J., Wiig, Ø., & Skaare, J. U. (2005). Does high organochlorine (OC) exposure impair the resistance to infection in polar bears (*Ursus maritimus*)? Part II: Possible effect of OCs on mitogen- and antigen-induced lymphocyte proliferation. *Journal of Toxicology and Environmental Health*, *Part A*, *68*, 457-484.

Lipscomb, T. P., Schulman, F. Y., Moffett, D., & Kennedy, S. (1994). Morbilliviral disease in an Atlantic bottlenose dolphin (*Tursiops truncatus*) from the Gulf of Mexico. *Journal of Wildlife Diseases*, *30*, 572-576.

Lommel, A., Kruse, H., Müller, E., & Wassermann, O. (1992). Organochlorine pesticides, octachlorostyrene, and mercury in the blood of Elb River residents, Germany. *Archives of Environmental Contamination and Toxicology*, *22*, 14-20.

Longnecker, M., Rogan, W., & Lucier, G. (1997). The human health effect of DDT (dichlorodiphenyltrichloroethane) and PCBs (polychlorinated diphenyls) and an overview of organochlorines in public health. *Annual Review of Public Health*, *18*, 211-244.

Lynn, S. K., & Würsig, B. (2002). Summer movement patterns of bottlenose dolphins in a Texas Bay. *Gulf of Mexico Science*, *20*(1), 25-37.

Marcovecchio, J. E., Moreno, V. J., Bastida, R. O., Gerpe, M. S., & Rodriquez, D. H. (1990). Tissue distribution of heavy metals in small cetaceans from the southwestern Atlantic Ocean. *Marine Pollution Bulletin*, *21*, 299-304.

Mariussen, E., & Fonnum, F. (2001). The effect of polychlorinated biphenyls on the high affinity uptake of the neurotransmitters dopamine, serotonin, glutamate and GABA, into rat brain synaptosomes. *Toxicology*, *159*, 11-21.

Mariussen, E., & Fonnum, F. (2003). The effect of brominated flame retardants on neurotransmitter uptake into rat brain synaptosomes and vesicles. *Neurochemistry International*, *43*, 533-542.

Mariussen, E., Andersen, J. M., & Fonnum, F. (1999). The effect of polychlorinated biphenyls on the uptake of dopamine and other neurotransmitters into rat brain synaptic vesicles. *Toxicology and Applied Pharmacology*, *161*, 274-282.

Marsili, L. (2000). Lipophilic contaminants in marine mammals: Review of the results of ten years' work at the Department of Environmental Biology, Siena University (Italy). *International Journal of Environment and Pollution*, *13*, 416-452.

Marsili, L., Fossi, M. C., Notarbartolo di Sciara, G., Zanardelli, M., Nani, B., Panigada, S., & Forcardi, S. (1998). Relationship between organochlorine contaminants and mixed function oxidase activity in skin biopsy specimens of Mediterranean fin whales (*Balaenoptera physalus*). *Chemosphere*, *37*, 1501-1510.

Matthews, J., & Zacharewski, T. (2000). Differential binding affinities of PCBs, HO-PCBs, and aroclors with recombinant human, rainbow trout (*Onchorhynkiss mykiss*), and green anole (*Anolis carolinensis*) estrogen receptors, using semi-high throughput competitive binding assay. *Toxicological Sciences*, *53*, 326-339.

Maze, K. S., & Würsig, B. (1999). Bottlenose dolphins of San Luis Pass, Texas: Occurrence patterns, site-fidelity, and habitat use. *Aquatic Mammals*, *25*(2), 91-103.

McCarty, L. S., & Munkittrick, K. R. (1996). Environmental biomarkers in aquatic toxicology: Fiction, fantasy, or functional? *Human Ecology Risk Assessment*, *2*, 268-274.

McDonald, T. A. (2002). A perspective on the potential health risks of PBDEs. *Chemosphere*, *46*, 745-755.

McFarlane, R. W., Bright, T. J., Cain, B. W., Hightower, C. M., Kendall, J. J., Kolb, J. W., Mueller, A. J., Sheridan, P. F., Smith, C. B., Wermund, E. G., & Whitledge, T. E. (1989). Issues and information needs. In T. E. Whitledge & S. M. Ray (Eds.), *Galveston Bay: Issues, resources, status, and management* (NOAA Estuary-of-the-Month Seminar Series No. 13). Washington, DC: NOAA. 114 pp.

McKinney, M. A., Arukwa, A., DeGuise, S., Martineau, D., Béland, P., Dallaire, A., Lair, S., LeBeuf, M., & Letcher, R. (2004). Characterization and profiling of hepatic P450 and phase II xenobiotic-metabolizing enzymes in beluga whales (*Delphinapterus leucas*) from the

St. Lawrence River Estuary and the Canadian arctic. *Aquatic Toxicology*, *69*, 35-49.

Meador, J. P., Ernest, D., Hohn, A. A., Tilbury, K., Gorzelany, J., Worthy, G., & Stein, J. E. (1999). Comparison of elements in bottlenose dolphins stranded on the beaches of Texas and Florida in the Gulf of Mexico over a one-year period. *Archives of Environmental Contamination and Toxicology*, *36*, 87-98.

Meironyté, D., Norén, K., & Bergman, Å. (1999). Analysis of polybrominated diphenyl ethers in Swedish human milk: A time-related trend study, 1972-1997. *Journal of Toxicology and Environmental Health*, *Part A*, *58*, 329-341.

Millie, D. F., Dionigi, C. P., Schofield, O., Kirkpatrick, G. J., & Tester, P. A. (1999). The importance of understanding the molecular cellular and ecophysiological bases of harmful algal blooms. *Journal of Phycology*, *35*, 1353-1355.

Minh, T. B., Nakata, H., Watanabe, M., Tanabe, S., Miyazaki, N., Jefferson, T. A., Prudente, M., & Subramanian, A. (2000). Isomer-specific accumulation and toxic assessment of polychlorinated biphenyls, including coplanar congeners, in cetaceans from the North Pacific and Asian coastal waters. *Archives of Environmental Contamination and Toxicology*, *39*, 398-410.

Morse, J. W., Presley, B. J., Taylor, R. J., Benoit, G., & Santschi, P. (1993). Trace metal chemistry of Galveston Bay: Water, sediments and biota. *Marine Environmental Research*, *36*, 1-37.

Murata, K., Budtz-Jørgensen, E., & Grandjean, P. (2004). Delayed brainstem auditory evoked potential latencies in 14-year-old children exposed to methylmercury. *Journal of Pediatrics*, *144*, 177-183.

Newell, C. J., Rifai, H. S., & Bedient, P. B. (1992). *Characterization of non-point sources and loadings of Galveston Bay* (Galveston Bay National Estuary Program publication GBNEP-15). Webster, TX: Galveston Bay National Estuary Program. 221 pp.

Newland, M. C., & Paletz, E. M. (2000). Animal studies of methylmercury and PCBs: What do they tell us about expected effects in humans? *Neurotoxicology*, *21*, 1003-1028.

Nigro, M., Campana, A., Lanzillotta, E., & Ferrara, R. (2002). Mercury exposure and elimination rates in captive bottlenose dolphins. *Marine Pollution Bulletin*, *44*, 1071-1075.

Norén, K., & Meironyté, D. (2000). Certain organochlorine and organobromine contaminants in Swedish human milk in perspective of past 20-30 years. *Chemosphere*, *40*, 1111-1123.

Odland, J. Ø., Deutch, B., Hansen, J. C., & Burkow, I. C. (2003). The importance of diet on exposure to and effects of persistent organic pollutants on human health in the Arctic. *Acta Paediatrica*, *92*, 1255-1266.

Ohta, S., Ishizuka, D., Nishimura, H., Nakao, T., Aozasa, O., Shimidzu, Y., Ochiai, F., Kida, T., Nishi, M., & Miyata, H. (2002). Comparison of polybrominated diphenyl ethers in fish, vegetables, and meats and levels in human milk of nursing women in Japan. *Chemosphere*, *46*, 689-696.

Olney, J. W. (2002). New insights and new issues in developmental neurotoxicology. *Neurotoxicology*, *23*, 659-668.

O'Shea, T. J. (1999). Environmental contaminants in marine mammals. In J. E. Reynolds, III & S. A. Rommel (Eds.), *Biology of marine mammals* (pp. 485-536). Washington, DC, and London: Smithsonian Institution Press. 578 pp.

O'Shea, T. J., Reeves, R. R., & Long, A. K. (Eds.). (1998). *Marine mammals and persistent ocean contaminants.* Proceedings of the Marine Mammal Commission Workshop, Keystone, Colorado, 12-15 October. 150 pp.

Patandin, S. (1999). *Effects of environmental exposure to polychlorinated biphenyls and dioxins on growth and development in young children.* Ph.D. thesis, Erasmus University, Rotterdam. (ISBN 90-9012306-7)

Peakall, D. B. (1999). Biomarkers as pollution indicators with special reference to cetaceans. *Journal of Cetacean Research and Management,* (Special Issue 1), 117-124.

Philbert, M., Billingsley, M. L., & Ruehl, K. R. (2000). Mechanisms of injury in the central nervous system. *Toxicologic Pathology*, *28*, 43-53.

Pierce, R. H., & Kirkpatrick, G. J. (2001). Innovative techniques for harmful algal toxin analysis. *Environmental Toxicology and Chemistry*, *20*, 107-114.

Porterfield, S. P. (2000). Thyroidal dysfunction and environmental chemicals—Potential impact on brain development. *Environmental Health Perspectives*, *108*(Supp. 3), 433-438.

Rayne, S., Ikonouou, M. G., Ross, P., Ellis, G., & Barreto-Lennard, L. G. (2004). PBDEs, PBBs and PCNs in three communities of free-ranging killer whales (*Orcinus orca*) from the Northeastern Pacific Ocean. *Environmental Science and Technology*, *38*, 4293-4299.

Reddy, M. L., Reif, J. S., Bachand, A., & Ridgway, S. H. (2001). Opportunities for using Navy marine mammals to explore associations between organochlorine contaminants and unfavorable effects on reproduction. *Science of the Total Environment*, *274*, 171-182.

Reese, E. R. (1987). Ontogeny of immunity in Inuit infants. *Arctic Medical Research*, *45*, 62.

Reeves, R. R., Rolland, R., & Clapham, P. J. (Eds.). (2001). *Causes of reproductive failure in North Atlantic right whales: New avenues of research* (Northeast Fisheries Science Center Reference Document 01-16). 46 pp.

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

Reijnders, P. J. H., Aguilar, A., & Donovan, G. P. (1999a). Planning workshop to develop a programme to investigate pollutant cause-effect relationships in cetaceans: "Pollution 2000+." *Journal of Cetacean Research and Management*, (Special Issue 1), 55-72.

Reijnders, P. J. H., Donovan, G. P., Aguilar, A., & Bjørge, A. (1999b). Report on the workshop on chemical pollution and cetaceans. *Journal of Cetacean Research and Management*, (Special Issue 1), 1-42.

Reijnders, P. J. H., Rowles, T., Donovan, G. P., O'Hara, T., Bjørge, A., Larsen, F., & Kock, K-H. (1999c). Pollution 2000+: After Barcelona. *Journal of Cetacean Research and Management*, (Special Issue 1), 77-82.

Rice, D., & Barone, S., Jr. (2000). Critical periods of vulnerability for the developing nervous system: Evidence from humans and animal models. *Environmental Health Perspectives*, *108*(Supp. 3), 511-533.

Rice, C. P., & Custer, T. W. (1991). The occurrence of chlorostyrenes in egrets and herons collected in Galveston Bay. In F. S. Shipley & R.W. Kiesling (Eds.), *Proceedings of the Galveston Bay Characterization Workshop, February 21-23, 1991* (Galveston Bay National Estuary Program publication GBNEP-6), Webster, TX: Galveston Bay National Estuary Program. 220 pp.

Richthoff, J., Rylander, L., Jonsson, B. A., Akesson, H., Hagmar, L., Nilsson-Ehle, P., Stridsberg, M., & Giwercman, A. (2003). Serum levels of 2,2',4,4',5,5'-hexachorobiphenyl (CB-153) in relation to markers of reproductive function in young males from the general Swedish population. *Environmental Health Perspectives*, *111*, 409-413.

Roditi-Elasar, M., Kerem, D., Hornung, H., Kress, N., Shoham-Frider, E., Goffman, O., & Spanier, E. (2003). Heavy metal levels in bottlenose and striped dolphins off the Mediterranean coast of Israel. *Marine Pollution Bulletin*, *46*, 491-521.

Rogan, W. J., Gladen, B. C., McKinney, J. D., Carreras, N., Hardy, P., Thullen, J., Tingelstad, J., & Tulley, M. (1986). Polychlorinated biphenyls (PCBs) and dichlorodiphenyl dichloroethene (DDE) in human milk: Effects of maternal factors and previous lactation. *American Journal of Public Health*, *76*, 172-177.

Ross, P. S. (1995). *Seals, pollution and diseases: Environmental contaminant-induced immunosuppression*. Den Haag, The Netherlands: CIP-Data Koninklijke Bibliotheek. 76 pp.

Ross, P. S. (2000). Marine mammals as sentinels in ecotoxicologic risk assessment. *Human Ecological Risk Assessment*, *6*, 29-46.

Ross, P. S., Ellis, G. M., Ikonomou, M. G., Barrett-Lennard, L. G., & Addison, R. F. (2000). High PCB concentrations in free-ranging Pacific killer whales, *Orcinus orca*: Effects of age, sex, and dietary preferences. *Marine Pollution Bulletin*, *40*, 504-515.

Rowland, L. P. (2000). Occupational and environmental neurotoxicology. In L. P. Rowland (Ed.), *Merritt's neurology* (pp. 940-948). Philadelphia: Lippincott, Williams, and Wilkins. 1,002 pp.

Rozati, R., Reddy, P. P., Reddanna, P., & Mujtaha, R. (2000). Xenoestrogens and male infertility: Myth or reality? *Asian Journal of Andrololology*, *2*, 263-269.

Sahlberg, C., Pohjanvirta, R., Gao, Y., Alaluusua, S., Tuomisto, J., & Lukinmaa P-L. (2002). Expression of the mediators of dioxin toxicity, aryl hydrocarbon receptor (AHR) and the AHR nuclear translocator (ARNT), is developmentally regulated in mouse teeth. *International Journal of Developmental Biology*, *46*, 295-300.

Sakamoto, M., Nakano, A., & Akagi, H. (2001). Declining Minamata male birth ratio associated with increased male fetal death due to heavy methylmercury pollution. *Environmental Research*, *87*(2), 92-98.

Salata, G. G. (1993). *Analysis of Gulf of Mexico marine mammals for organochlorine pesticides and PCBs.* M.Sc. thesis, Texas A&M University, College Station, TX. 134 pp.

Salata, G. G., Wade, T. L., Sericano, J. L., Davis, J. W., & Brooks, J. M. (1995). Analysis of Gulf of Mexico bottlenose dolphins for organochlorine pesticides and PCBs. *Environmental Pollution*, *88*, 167-175.

Sandau, C. D., Ayotte, P., Dewailly, E., Duffe, J., & Norstrom, J. (2000). Analysis of hydroxylated metabolites of PCBs (OH-PCBs) and other chlorinated phenolic compounds in whole blood from Canadian Inuit. *Environmental Health Perspectives*, *108*, 611-616.

Sandau, C. D., Ayotte, P., Dewailly, E., Duffe, J., & Norstrom, J. (2002). Pentachlorophenol and hydroxylated polychlorinated biphenyl metabolites in umbilical cord plasma of neonates from coastal populations in Quebéc. *Environmental Health Perspectives*, *110*, 411-417.

Santschi, P. H., Presley, B. J., Wade, T. L., Garcia-Romero, B., & Baskaran, M. (2001). Historical contamination of PAHs, PCBs, DDTs, and heavy metals in Mississippi River Delta, Galveston Bay, and Tampa Bay sediment cores. *Marine Environmental Research*, *52*, 51-79.

Sarokin, D., & Schulkin, J. (1992). The role of pollution in large-scale population disturbances. Part 1: Aquatic populations. *Environmental Science and Technology*, *26*, 1476-1484.

Scholin, C., Gulland, F., Doucette, G. J., Benson, S., Busman, M., Chavez, F. P., Cordaro, J., DeLong, R., De Vogelaere, A., Harvey, J., Haulena, M., Lefebvre, K., Lipscomb, T., Loscutgoff, S., Lowenstine, L. J., Marin, R., III, Miller, P. E., McLellan, W. A., Moeller, P. D. R., Powell, C. L., Rowles, T., Silvagni, P., Silver, M., Spraker, T., Trainer, V., & Van Dolah, F. M. (2000). Mortality of sea lions along the central California coast linked to a toxic diatom bloom. *Nature*, *403*, 80-84.

Schwartz, P. M., Jacobson, S. W., Gein, G., Jacobson, J. L., & Price, H. A. (1983). Lake Michigan fish consumption as a source of polychlorinated biphenyls in human cord serum, maternal serum, and milk. *American Journal of Public Health*, *73*, 293-296.

Segar, D. A., & Stamman, E. (1986). A strategy for design of marine pollution monitoring studies. *Water Science and Technology*, *18*, 15-26.

Serajee, F. J., Nabi, R., Zhong, H., & Huq, M. (2004). Polymorphisms in xenobiotic metabolism genes and autism. *Journal of Child Neurology*, *19*(6), 413-417.

Shane, S. H. (1990). Comparison of bottlenose dolphin behavior in Texas and Florida, with a critique of methods for studying dolphin behavior. In S. Leatherwood & R. R. Reeves (Eds.), *The bottlenose dolphin* (pp. 541-558). San Diego: Academic Press. 653 pp.

Shaw, G. R., & Connell, D. W. (2001). DNA adducts as a biomarker of polycyclic aromatic hydrocarbon exposure

in aquatic organisms: Relationship to carcinogenicity. *Biomarkers*, *6*, 64-71.

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.

Sheridan, P. F., Slack, R. D., Ray, S. M., McKinney, L. W., Klima, E. F., & Calnan, T. R. (1989). Biological components of Galveston Bay. In T. E. Whitledge & S. M. Ray (Eds.), *Galveston Bay: Issues, resources, status, and management* (NOAA Estuary-of-the-Month Seminar Series No. 13). Washington, DC: NOAA. 114 pp.

Silvagni, P. A., Lowenstine, L. J., Spaker, T., Lipscomb, T. P., & Gulland, F. M. D. (2005). Pathology of domoic acid toxicity in California sea lions (*Zalophus californianus*). *Veterinary Pathology*, *42*, 184-191.

Sjödin, A., Hagmar, L., Klasson-Wehler, E., Björk, J., & Bergman, A. (2000). Influence of the consumption of fatty Baltic Sea fish on plasma levels of halogenated environmental contaminants in Latvian and Swedish men. *Environmental Health Perspectives*, *108*, 1035-1041.

Skaare, J. U., Bernhoft, A., Wiig, Ø. W., Norum, K. R., Haug, E., Eide, D. M., & Derocher, A. E. (2001). Relationships between plasma levels of organochlorines, retinol and thyroid hormones from polar bears (*Ursus maritimus*) at Svalbar. *Journal of Toxicology and Environmental Health A*, *62*, 227-241.

Smith, A. G., Carthew, P., Francis, J. E., & Ingebrigtsen, K. (1994). Influence of iron on the induction of hepatic tumors and porphyria by octachlorostyrene in C57BL/10cSn mice. *Cancer Letters*, *81*, 145-150.

Smultea, M. A., & Würsig, B. (1995). Behavioral reactions of bottlenose dolphins to the *Mega Borg* oil spill, Gulf of Mexico, 1990. *Aquatic Mammals*, *21*, 171-181.

Stridh, H., Gigliotti, D., Orrenius, S., & Cotgreave, I. (1999). The role of calcium in pre- and post mitochondrial events in tributyltin-induced T-cell apoptosis. *Biochemical and Biophysical Research Communications*, *266*, 460-465.

Stridh, H., Cotgreave, I., Müller, M., Orrenius, S., & Gigliotti, D. (2001). Organotin-induced caspase activation and apoptosis in human peripheral blood lymphocytes. *Chemical Research in Toxicology*, *14*, 791-798.

Struntz, W. D. J., Kucklick, J. R., Schantz, M. M., Becker, P. R., McFee, W. E., & Stolen, M. K. (2004). Persistent organic pollutants in rough-toothed dolphins (*Steno bredanensis*) sampled during an unusual mass stranding event. *Marine Pollution Bulletin*, *48*, 164-192.

Svensson, B-G., Hallberg, T., Nilsson, A., Schütz, A., & Hagmar, L. (1994). Parameters of immunological competence in subjects with high consumption of fish contaminated with persistent organochlorine compounds. *International Archives of Occupational and Environmental Health*, *65*, 351-358.

Svensson, B-G., Nilsson, A., Hansson, M., Rappe, C., Åkesson, B., & Skerfving, S. (1991). Exposure to dioxins and dibenzofurans through the consumption of fish. *New England Journal of Medicine*, *324*, 8-12.

Sweet, L. I., & Zelikoff, J. T. (2001). Toxicology and immunotoxicology of mercury: A comparative review in fish and humans. *Journal of Toxicology and Environmental Health B*, *4*, 161-205.

Szefer, P., Zdrojewska, I., Jensen, J., Lockyer, C., Skóra, K., Kuklik, I., & Malinga, M. (2002). Intercomparison studies on distribution of heavy metals in liver, kidney, and muscle of harbor porpoise, *Phocoena phocoena*, from southern Baltic Sea and coastal waters of Denmark and Greenland. *Archives of Environmental Contamination and Toxicology*, *42*, 508-522.

Takahashi, S., Le, L. T. H., Saeki, H., Nakatani, N., Tanabe, S., Miyazaki, N., & Fujise, Y. (2000). Accumulation of butyltin compounds and total tin in marine mammals. *Water Science and Technology*, *42*, 97-108.

Tanabe, S. (1988). PCB problems in the future: Foresight from current knowledge. *Environmental Pollution*, *50*, 5-28.

Tanabe, S. (2002). Contamination and toxic effects of persistent endocrine disrupters in marine mammals and birds. *Marine Pollution Bulletin*, *45*, 69-77.

Tanabe, S., Iwata, H., & Tatskawa, R. (1994). Global contamination by persistent organochlorines and their ecotoxicological impact on marine mammals. *Science of the Total Environment*, *154*, 163-177.

Tanabe, S., Kannan, N., Subramanian, A., Watanabe, S., & Tatsukawa, R. (1987). Highly toxic coplanar PCBs: Occurrence, source, persistency, and toxic implications to wildlife and humans. *Environmental Pollution*, *47*, 147-163.

Tarkpea, M., Hagen, I., Carlberg, G. E., Kolsaker, P., & Storflor, H. (1985). Mutagenicity, acute toxicity, and bioaccumulation potential of six chlorinated styrenes. *Bulletin of Environmental Contamination and Toxicology*, *35*, 525-530.

Teitelbaum, J. S., Zatorre, R. J., Carpenter, S., Gendron, D., Evans, A. C., Gjedde, A., & Cashman, N. R. (1990). Neurologic sequelae of domoic acid intoxication due to the ingestion of contaminated mussels. *New England Journal of Medicine*, *322*, 1781-1787.

Thibodeaux, J. R., Hanson, R. G., Rogers, J. M., Grey, B. E., Barbee, B. D., Richard, J. H., Butenhoff, J. L., Stevenson, L. A., & Lau, C. (2003). Exposure to perfluorooctane sufonate during pregnancy in rat and mouse. I. Maternal and prenatal evaluations. *Toxicological Sciences*, *74*, 369-381.

Tilson, H. A. (2000). New horizons: Future directions in neurotoxicology. *Environmental Health Perspectives*, *108*(Supp. 3), 439-441.

Tilson, H. A., & Kodavanti, R. S. (1998). The neurotoxicity of polychlorinated biphenyls. *Neurotoxicology*, *19*, 517-526.

Tilson, H. A., Jacobson, J. L., & Rogan, W. J. (1990). Polychlorinated biphenyls and the developing nervous system: Cross species comparisons. *Neurotoxicology and Teratology*, *12*, 239-248.

Trask, C. L., & Kosofsky, B. E. (2000). Developmental considerations of neurotoxic exposure. *Clinical Neurobehavioral Toxicology*, *18*, 541-561.

Tuerk, K. J. S., Kucklick, J. R., Becker, P. R., Stapleton, H. M., & Baker, J. E. (2005). Persistent organic pollutants in two dolphin species with focus on toxaphene and polybrominated diphenyl ethers. *Environmental Science and Technology*, *39*, 692-698.

Turnbull, B. S. (1998). *Tissue levels of essential and non-essential metals and their associations with pathological and microbiological findings in Atlantic bottlenose dolphins* (Tursiops truncatus). Ph.D. dissertation, The University of Texas Medical Branch at Galveston. 397 pp.

Tyler, C. R., Jobling, S., & Sumpter, J. P. (1998). Endocrine disruption in wildlife: A critical review of the evidence. *Critical Reviews in Toxicology*, *28*, 319-361.

Van Bressem, M-F., Gaspar, R., & Aznar, F. J. (2003). Epidemiology of tattoo skin disease in bottlenose dolphins *Tursiops truncatus* from the Sado Estuary, Portugal. *Diseases of Aquatic Organisms*, *56*, 171-179.

Van Bressem, M-F., Van Waerebeek, K., & Raga, J. A. (1999). A review of virus infections of cetaceans and the potential impact of morbilliviruses, poxviruses and papillomaviruses on host population dynamics. *Diseases of Aquatic Organisms*, *38*, 53-65.

Van Bressem, M-F., Van Waerebeek, K., Jepson, P. D., Raga, J. A., Duignan, P. J., Nielsen, O., De Beneditto, A. P., Siciliano, S., Ramos, R., Kant, W., Peddemors, V., Kinoshita, R., Ross, P. S., López-Fernandez, A., Evans, K., Crespo, K. E., & Barrett, T. (2001). An insight into the epidemiology of dolphin morbillivirus worldwide. *Veterinary Microbiology*, *81*, 287-304.

Van den Berg, M., Birnbaum, L., Bosveld, A. T. C., Brunström, B., Cook, P., Freeley, M., Giesy, J. P., Hanberg, A., Hasegawa, R., Kennedy, S. W., Kubiak, T., Larsen, J. C., van Leeuwen, F. X., Liem, A. K. D., Nolt, C., Peterson, R. E., Poellinger, L., Safe, S., Schrenk, D., Tillitt, D., Tysklind, M., Younes, M., Waern, F., & Zacharewski, T. (1998). Toxic equivalency factors (TEFs) for PCBs, PCDDs, PCDFs for humans and wildlife. *Environmental Health Perspectives*, *106*, 775-792.

Van Dolah, F. M. (2000). Marine algal toxins: Origins, health effects, and their increased occurrence. *Environmental Health Perspectives*, *108*(Supp. 1), 133-141.

Viberg, H., Fredriksson, A., Jakobsson, E., Örn, U., & Eriksson, P. (2003). Neurobehavioral derangements in adult mice receiving decabrominated diphenyl ether (PBDE 209) during a defined period of neonatal brain development. *Toxicological Sciences*, *76*, 112-120.

Vogelgesang, J., Kypke-Hutter, K., Malisch, R., Binnemann, P., & Dietz, W. (1986). The origin of a contamination of fish from the river Neckar with hexachlorobenzene, octachlorostyrene, and pentachlorostyrene: Formation in an industrial process. *Zeitschrift fur Lebensmittel-Untersuchung und-Forschung*, *182*, 464-470.

Vojdani, A., Pangborn, J. B., Vojdani, E., & Cooper, E. L. (2003). Infections, toxic chemicals and dietary peptides binding to lymphocyte receptors and tissue enzymes are major instigators of autoimmunity in autism. *International Journal of Immunopathology and Pharmacology*, *16*(3), 189-199.

Waalkes, W. P. (2000). Cadmium carcinogenesis in review. *Journal of Inorganic Chemistry*, *79*, 241-244.

Wade, T. L., Hwang, H-M., Qian, Y., Sweet, T., & Sericano, J. L. (2001). *Lysosomal destabilization: Indicators of environmental degradation in Galveston Bay, Texas.* Galveston Bay Estuary Program State of the Bay Symposium V, Galveston, TX.

Wania, F., & Mackay, D. (1993). Global fractionation and cold condensation of low volatility organochlorine compounds in polar regions. *Ambio*, *22*, 10-18.

Watanabe, M., Kannan, K., Takahashi, A., Loganathan, B. G., Odell, D. K., Tanabe, S., & Giesy, J. P. (2000). Polychlorinated biphenyls, organochlorine pesticides, tris(4-chorophenyl)methane, and tris (4-chorophenyl)methanol in livers of small cetaceans stranded along Florida coastal waters, USA. *Environmental Toxicology and Chemistry*, *19*, 1566-1574.

Weisglas-Kuperus, N., Papandin, S., Berbers, G. A. M., Sas, T. C. J., Mulder, P. G. H., Sauer, P. J. J., & Hooijkaas, H. (2000). Immunologic effects of background exposure to polychlorinated biphenyls and dioxins in Dutch preschool children. *Environmental Health Perspectives*, *108*, 1203-1207.

Weller, D. W. (1998). *Global and regional variation in the biology and behavior of bottlenose dolphins.* Ph.D. dissertation, Texas A&M University, College Station, TX. 142 pp.

Wells, R. S. (1991). Bringing up baby. *Natural History*, *100*, 56-62.

Wells, R. S., Scott, M. D., & Irvine, A. B. (1987). The social structure of free-ranging bottlenose dolphins. In H. H. Genoways (Ed.), *Current mammalogy* (pp. 247-304). New York: Plenum Press.

Wells, R. S., Hansen, L. J., Baldridge, A., Dohl, T. P., Kelly, D. L., & Defran, R. H. (1990). Northward extension of the range of bottlenose dolphins along the California coast. In S. Leatherwood & R. R. Reeves (Eds.), *The bottlenose dolphin* (pp. 421-431). San Diego: Academic Press. 653 pp.

Whalen, M. M., Green, S. A., & Loganathan, B. G. (2002). Brief butyltin exposure induces irreversible inhibition of the cytotoxic function on human natural killer cells, in vitro. *Environmental Research*, *88*, 19-29.

Whalen, M. M., & Loganathan, B. G. (2001). Butyltin exposure causes a rapid decrease in cyclic AMP levels in human lymphocytes. *Toxicology and Applied Pharmacology*, *171*, 141-148.

Whalen, M. M., Loganathan, B. G., & Kannan, K. (1999). Immunotoxicity of environmentally relevant concentrations of butyltins on human natural killer cells in vitro. *Environmental Research*, *81*(Section A), 108-116.

Wilson, B., Grellier, K., Hammond, P. S., Brown, G., & Thompson, P. M. (2000). Changing occurrence of epidermal lesions in wild bottlenose dolphins. *Marine Ecology Progress Series*, *205*, 283-290.

Wilson, B., Arnold, H., Bearzi, G., Fortuna, C. M., Gaspar, R., Ingram, S., Liret, C., Pribanic, S., Read, A. J., Ridoux, V., Schneider, K., Urian, K. W., Wells, R. S., Wood, C., Thompson, P. M., & Hammond, P. S. (1999). Epidermal diseases in bottlenose dolphins: Impacts of natural and anthropogenic factors. *Proceedings of the Royal Society of London – Series B: Biological Sciences, 266*, 1077-1083.

Wolkers, H., Van Bavel, B., Derocher, A. E., Wiig, Ø., Kovacs, K. M., Lydersen, C., & Gindström, G. (2004). Congener-specific accumulation and food chain transfer of polybrominated diphenyl esters in two Arctic food chains. *Environmental Science and Technology*, *38*, 1667-1674.

Worthy, G. (1998). Patterns of bottlenose dolphin, *Tursiops truncatus*, strandings in Texas. In R. Zimmerman (Ed.), *Characteristics and causes of Texas marine strandings* (NOAA Technical Report to NMFS 143). Washington, DC: U.S. Department of Commerce. 85 pp.

Würsig, B. (1991). Advice to dolphins: Avoid the nets and PCBs underwater, and don't breathe the air. In P. G. H. Evans (Ed.), *European research on cetaceans. Volume 5: Proceedings of the fifth annual conference of the European Cetacean Society.* Sandefjord, Norway and Cambridge, England.

Würsig, B., & Harris, G. (1990). Site and association fidelity in bottlenose dolphins off Argentina. In S. Leatherwood & R. R. Reeves (Eds.), *The bottlenose dolphin* (pp. 361-365). San Diego: Academic Press. 653 pp.

Yamabe, Y., Hoshino, A., Imura, N., Suzuki, T., & Himeno, S. (2000). Enhancement of androgen-dependent transcription and cell proliferation by tributyltin and triphenyltin in human prostate cancer cells. *Toxicology and Applied Pharmacology*, *169*, 177-184.

Ylitalo, G. M., Matkin, C. O., Buzitis, J., Krahan, M., Jones, L. L., Rowles, T., & Stein, J. E. (2001). Influence of life-history parameters on organochlorine concentrations in free-ranging killer whales (*Orcinus orca*) from Prince William Sound, AK. *Science of the Total Environment*, *281*, 183-203.