Possible Mechanisms of Action of Environmental Contaminants on St. Lawrence Beluga Whales (*Delphinapterus leucas*)

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A small isolated population of beluga whales (*Delphinapterus leucas*) that are highly contaminated by pollutants, mostly of industrial origin, resides in the St. Lawrence estuary, Québec, Canada. Overhunting in the first half of the century was the probable cause for this population to dwindle from several thousand animals to the current estimate of 500. The failure of the population to recover might be due to contamination by organochlorine compounds, which are known to lead to reproductive failure and immunosuppression in domestic and laboratory animals and seals. Functional and morphological changes have been demonstrated in thyroid gland and adrenal cortex in many species exposed to organochlorinated compounds, including seals. Morphological lesions, although different, were also found in belugas. Functional evaluation of thyroid and adrenal glands of contaminated (St. Lawrence) versus much less contaminated (Arctic) belugas is currently under way. Necropsy of St. Lawrence belugas showed numerous severe and disseminated infections with rather mildly pathogenic bacteria, which suggests immunosuppression. Organochlorine compounds and other contaminants found in beluga whales cause immunosuppression in a variety of animal species including seals. Thirty-seven percent of all the tumors reported in cetaceans were observed in St. Lawrence beluga whales. This could be explained by two different mechanisms: high exposure to environmental carcinogens and suppression of immunosurveillance against tumors. Overall, St. Lawrence belugas might well represent the risk associated with long-term exposure to pollutants present in their environment and might be a good model to predict health problems that could emerge in highly exposed human populations over time. — Environ Health Perspect 103(Suppl 4):73–77 (1995)

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Introduction

A small population of beluga whales (*Delphinapterus leucas*) resides in the St. Lawrence estuary. From 5000 animals at the beginning of the century (*1*), the population has been reduced to approximately 500 (*2*) and has been listed as an endangered population (*3*). After the decline initiated in the early 20th century by overhunting, several hypotheses have been put forward to account for the failure of this population to recover during the last 40 years.

High concentrations of organochlorines, as well as benzo[*a*]pyrene (B[*a*]P) exposure, have been demonstrated in the tissues of these animals (*4,5*); the concentrations of polychlorinated biphenyls (PCBs), dichlorophenyl trichloroethane (DDT), Mirex, mercury, and lead were much higher than those found in Arctic belugas (*6,7*).

Postmortem examination of carcasses retrieved from the shores of the St. Lawrence since 1982 has shown a high prevalence of degenerative, infectious, hyperplastic, or necrotic lesions often associated with mildly pathogenic organisms, in addition to a very high prevalence of neoplasms (*5,8,9*). The frequency and severity of the lesions described in this population were considerably higher than what has been found in marine mammals elsewhere. Consequently, a link was suggested between toxic contaminants in the St. Lawrence basin food web and the precarious state of the population. The present article describes the possible relationships between the high levels of environmental contaminants in St. Lawrence beluga whale tissues and the various lesions contributing to mortality and to decreased reproduction in this population, with regard to what is known in other species of marine mammals, laboratory animals, and humans.

Reproductive System

It is well known that reproductive functions can be altered by the presence of environmental contaminants, and numerous mechanisms have been proposed, from the proestrogenic effect of some PCB congeners, to the more subtle transgenerational effects (*10*).

In marine mammals, reproductive failure has been suspected in declining populations of seals inhabiting highly polluted ecosystems, and a link was proposed between reproductive failure and pollution (*11*). Uterine stenoses and occlusions were reported in different populations of seals in

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association with high PCB loads (*12–14*). Premature births in California sea lions (*Zalophus californianus*) have also been associated with high levels of organochlorines (*15*). Dall's porpoises (*Phocoenoides dalli*) from the northwestern North Pacific showed reduced testosterone levels in relation with high PCB and DDE concentrations (*16*). In humans, it has been suggested that reduced sperm count could be the result of exposure to estrogenic pollutants during pregnancy (*17*). Most of these associations between reproductive failure and pollution were circumstantial, but a more recent experimental study demonstrated that seals fed polluted fish showed reduced pup production when compared to those fed much less polluted fish (*18*).

In St. Lawrence beluga whales, a reduced reproductive rate, possibly associated with contamination, is suspected because the unexploited population has not increased in the last 10 years (*4,19*). Population modeling indicates that the observed stable population likely results from decreased reproduction and decreased survival of juveniles (*19*). Mature spermatozoa were observed on histological sections of testes of all adult males (De Guise et al., unpublished observations), but viability, motility, counts, and the absence or presence of abnormalities, criteria that can be affected by organochlorines in humans (*17,20*) could not be assessed. The number of pregnant females appeared dramatically low in St. Lawrence belugas, and a quantitative study of the cyclic corpuscules on serial sections of ovaries demonstrated little ongoing ovarian activity compared to what is reported in Arctic belugas (*21,22*). An adult hermaphrodite beluga was found with two ovaries, two testes, and complete genital tracts of both sexes with the exception of cervix, vagina, and vulva (*23*). This was only the fourth mammal ever reported with two separate gonads of each sex (*23*). In view of the multiple developmental effects of pollutants with estrogenic activity (*10*), this phenomenon may be related to pollution.

Endocrine System

Thyroid

The thyroid gland appears to be a rather well-defined target of PCB exposure. Altered levels of circulating thyroid hormones (*24*) and morphological changes in the thyroid gland (*25*) have been demonstrated in rats exposed to PCBs. Histological lesions (colloid depletion and interstitial fibrosis) were also found in thyroid glands of harbor seals (*Phoca vitulina*) in the North Sea during the phocine distemper epizootics and in harbor porpoises (*Phocoena phocoena*) from the same waters. Both of these species were contaminated with high concentrations of PCBs, as compared to the less contaminated harbor seals from Iceland (*26*). In another study, harbor seals fed PCB-contaminated fish from the Wadden Sea had decreased concentrations of plasma retinol (vitamin A) and thyroid hormones when compared to seals fed fish from the Atlantic (low levels of PCBs) (*27*). No clear evidence of thyroid changes similar to those described in seals and porpoises were found in St. Lawrence belugas. It should be noted that subtle differences should be interpreted with care because seasonal variations have been demonstrated in thyroid morphology and secretion in Arctic beluga whales (*28*). However, other lesions were found in St. Lawrence animals including abscesses in the thyroid, an uncommon finding in other species, and two small thyroid adenomas in one animal. The circulating levels of thyroid hormones and vitamin A of highly contaminated St. Lawrence belugas are currently being compared to much less contaminated Arctic belugas that have already been sampled and analyzed.

Adrenals

Adrenal glands are also affected by organochlorines in some laboratory animals. Bergman and Olsson (*29*) reported adrenal hyperplasia in grey seals (*Halichoerus grypus*) and ringed seals (*Phoca hispida*) in the Baltic Sea, which they associated with the high loads of organochlorine pollutants observed in these populations. More recently, abnormally high concentrations of organochlorines were demonstrated in adrenals of rodents, birds, and seals, and metabolites were found to bind covalently to adrenal cortex cells where their toxicity was expressed (*30*). These binding and toxic characteristics varied in different species (*30*).

Two types of lesions affected the adrenal cortex of St. Lawrence belugas: hyperplastic nodules and serous cysts (*9*). Morphologically, the nodules appear as intermediate between hyperplastic foci and adenomas, according to the classification criteria used for domestic animals, rats, and humans (*31–33*). However, such a high incidence of adenomas in a single population would appear unusual. Whether these nodules are functional or not is still unknown. Serous cysts have apparently never been described in domestic animals, but similar lesions were reported in female white-sided dolphins (*Lagenorhynchus acutus*) (*34*). These lesions presumably reflect a functional alteration of the physiology of the adrenal cortex. The pathophysiology proposed for the development of cysts in the adrenal cortex of beluga whales (*9*) involving hydropic degeneration of clusters of adrenocortical cells, could correspond to an exaggeration of the adrenocorticolytic process as described under DDT metabolite exposure (*30*). Circulating levels of corticosteroids in highly contaminated St. Lawrence belugas, compared to much less contaminated Arctic belugas, are currently being investigated in the course of a study on immunotoxicology. An investigation is planned to determine the presence of DDT metabolites in adrenal glands and the presence of any potentially adrenocorticolytic compound in the blubber (reflecting exposure) of St. Lawrence belugas.

Immune Functions

Ample evidence that organohalogens have detrimental effects on the immune system of man and animals has been collected over the past two decades. These compounds alter the functions of both arms of the immune system, cellular and humoral immunity. 2,3,7,8,-Tetrachlorodibenzo-*p*-dioxin (TCDD), the most immunotoxic of aromatic halogenated hydrocarbons, induces thymic atrophy in most experimental species (*35–38*). PCBs, and most notably the coplanar congeners, have similar, albeit less severe, effects; they cause lymphoid depletion in chicks (*35*), reduce natural cell toxicity in rats (*39,40*), decrease the number of T cells and the T helper/T suppressor cell ratio in nonhuman primates (*41*), and reduce T cell-mediated cytotoxic activity in mice (*37*). PCBs decrease antibody production in response to injection of sheep red blood cells (SRBC) in PCB-treated mice and nonhuman primates (*41–43*). A reduction of serum IgA levels seems to be a consistent component of PCB immunotoxicity (*42,44,45*). B cells and particularly B cell differentiation are emerging as important targets for halogenated hydrocarbons (*36*). Serum corticosteroid levels are also altered by PCBs (*37,46,47*). The immunotoxicity of various metabolites of PCBs has also been demonstrated; chlorinated diphenyl ethers, found in Great Lakes fish, significantly decrease circulating lymphocytes in male rats (*48*).

It is not surprising that PCB-induced immunosuppression results in a higher

sensitivity of experimental animals to a wide variety of infectious agents: gram-negative bacteria (or their endotoxins), protozoa, and viruses. The sensitivity of PCB-treated mice to endotoxin, malaria (*44*), and bacteria (*43*) is increased; rabbits synthesize less antibodies after being challenged by pseudorabies virus (*49*), and mice are more sensitive to challenge by Herpes simplex and ectromelia (mousepox) (*50*); the resistance of PCB-treated ducks to duck hepatitis virus is also impaired (*51*). Similarly, the complement system, a nonspecific defense mechanism against infectious agents, is altered by PCBs (*52*).

Studies on other pesticides confirm this xenobiotic-related immunosuppression of humoral and cellular responses as well as the decrease in natural resistance to viral and bacterial infections (*53–55*). Immune humoral (*53,54,56,57*) and cellular (*58,59*) responses to dieldrin, one of the most potent immunosuppressive insecticides (*53*), were examined after intoxication of inbred mouse strains with different natural resistance to selected pesticides. The data showed that single sublethal doses of dieldrin inhibited the number of SRBC-primed cells (*53,57*). Similar patterns of dieldrin-induced immunosuppression of the primary IgM response to thymo-dependent and T cell-independent antigens were observed, suggesting a dysfunction of cellular cooperation during the induction phase of the immune response (*57*). Exposure to single sublethal doses of dieldrin, however, resulted in transient inhibition only of mixed lymphocyte reactivity (MLR) and in abrogation of graft-versus-host reaction at a time of maximal MLR inhibition, but in no other visible damage of T cell functions or cell viability (*58,59*).

The immunotoxic potential of dieldrin was clearly shown in *in vivo* models of viral infection with mouse hepatitis virus (MHV3) (*53,54,56,60*) and of bacterial infection with *Salmonella typhimurium* (*61*). Decreased macrophage phagocytic (*54*) and bactericidal (*62*) activities were observed following single, sublethal exposures to dieldrin, and impairment of macrophage antigen processing by dieldrin was observed in a model of antigen processing (avidin) by the cells (*55*). These data showed that exposure to pesticides can affect immune defense mechanisms and, to some extent, the natural antiviral and antibacterial resistance of the host.

Recently, seals experimentally fed polluted fish from the Baltic Sea demonstrated suppression of immune functions when compared to seals fed clean fish from the Atlantic Ocean (*63*). This was the first experimental demonstration in semifield conditions of effects of a mixture of contaminants at levels encountered in the environment on immune functions of marine mammals. The frequent infections with mildly pathogenic bacteria found in St. Lawrence belugas strongly suggest immunosuppression that could be related to the high concentrations of environmental contaminants found in their tissues. A study to correlate an eventual immunosuppression of beluga whales to levels of contamination in St. Lawrence versus Arctic animals is currently under way (*64,65*).

Tumors

Overall, worldwide a total of 75 tumors have been reported in cetaceans; 28 (37%) come from 18 animals out of 45 necropsies of St. Lawrence beluga whales that were collected since 1982 from a population of only around 500 animals (40% of the animals had at least one tumor) (*8*). Excluding gastric papillomas that were attributed to papillomaviruses (*66*), the cause of the tumors observed in St. Lawrence belugas is unknown. Two factors could have contributed to such a high prevalence of neoplasms in that single population: exposure to carcinogenic compounds and decreased resistance to the development of tumors.

Thoughout their lives, St. Lawrence belugas are exposed to various toxic compounds, some of which are well known carcinogens. B[*a*]P, to which St. Lawrence whales are exposed (*5,67*), is among the more potent genotoxic carcinogens found commonly in contaminated environments, acting as an initiator (*68,69*). Others, such as PCBs, are recognized as promoters of tumors in initiated cells (*68*). Numerous compounds that are not directly carcinogenic can induce hyperplasia, which was recently pointed out as an important event in carcinogenesis (*70*). Preconception exposure of parental germinal cells or exposure of fetal somatic cells *in utero* to chemicals that would provide the first step in carcinogenesis (known as initiation), followed by postnatal exposure to tumor promoters, would result in increased incidence of tumors, with possible transgenerational effects of carcinogens (*71*). This feature of chemical carcinogenesis should be investigated as a possible contributing factor to the high prevalence of neoplasms in St. Lawrence belugas. Should transgenerational effects be involved, the prevalence of tumors could stay high for a long period of time because high burdens of lipophilic pollutants are carried by females and transferred to offspring through the placenta and milk in this species (De Guise et al., unpublished data) (*4*).

Decreased resistance to the development of tumors could also be an important contributing factor. Higher prevalence of lymphoreticular, DNA virus-induced, and chemical carcinogen-induced neoplasms was found in nonspecifically immunodeficient hosts (*68,72,73*), athymic mice (nude mice), and beige mice, respectively, demonstrating the role of the immune system as a whole, and of T lymphocytes and Natural Killer (NK) cells in immune surveillance for tumors. NK activity, among others, may be influenced by a variety of factors (*8*), some of which may be specifically influenced by contaminants found in the tissues of belugas. For example, concentrations of estrogens and vitamin A and its precursors, which can be altered by PCBs and DDT (*74*), may in turn influence NK activity (*75–77*). In addition, PCBs are direct immunosuppressors (*78*).

Conclusion

High concentrations of a complex mixture of ubiquitous pollutants were found in tissues of St. Lawrence beluga whales. Among these chemicals, many were demonstrated to have adverse effects on different aspects of the normal physiology of various species of animals, most often in laboratory animals. Many of the effects demonstrated experimentally were also observed in other highly exposed species of animals and humans in their own environments where cause–effect links were strongly suspected. The highly exposed St. Lawrence beluga whales also exhibited lesions in most of the target systems identified in toxicological studies of other species of marine and land mammals, as well as humans. This long-lived (30 years) species appears to reflect particularly well the risks associated with life in a polluted ecosystem. We propose it as a model for potential long-term consequences of pollution on human health.

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