Cancer in Wildlife, a Case Study: Beluga from the St. Lawrence Estuary, Québec, Canada

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A population of approximately 650 beluga (*Delphinapterus leucas*) inhabits a short segment of the St. Lawrence estuary (SLE). Over 17 years (1983–1999), we have examined 129 (or 49%) of 263 SLE beluga carcasses reported stranded. The major primary causes of death were respiratory and gastrointestinal infections with metazoan parasites (22%), cancer (18%), and bacterial, viral, and protozoan infections (17%). We observed cancer in 27% of examined adult animals found dead, a percentage similar to that found in humans. The estimated annual rate (AR) of all cancer types (163/100,000 animals) is much higher than that reported for any other population of cetacean and is similar to that of humans and to that of hospitalized cats and cattle. The AR of cancer of the proximal intestine, a minimum figure of 63 per 100,000 animals, is much higher than that observed in domestic animals and humans, except in sheep in certain parts of the world, where environmental contaminants are believed to be involved in the etiology of this condition. SLE beluga and their environment are contaminated by polycyclic aromatic hydrocarbons (PAHs) produced by the local aluminum smelters. The human population living in proximity of the SLE beluga habitat is affected by rates of cancer higher than those found in people in the rest of Québec and Canada, and some of these cancers have been epidemiologically related to PAHs. Considered with the above observations, the exposure of SLE beluga to PAHs and their contamination by these compounds are consistent with the hypothesis that PAHs are involved in the etiology of cancer in these animals. *Key words:* aluminum, beluga, cancer, cetaceans, pollution, polycyclic aromatic hydrocarbons, whale, wildlife. *Environ Health Perspect* 110:285–292 (2002). [Online 12 February 2002]

http://ehpnet1.niehs.nih.gov/docs/2002/110p285-292martineau/abstract.html

The St. Lawrence River estuary (SLE), Québec, Canada, receives the effluent from one of the most industrialized regions of the world (Figure 1). It is inhabited by the southernmost population of beluga (*Delphinapterus leucas*), a population unique in its accessibility to investigation and its geographic isolation from the Arctic habitat where the other populations of beluga are found. The SLE beluga population has dwindled from an estimated 5,000 to the current estimated 600–700 animals, in part because of the hunting pressure that continued until 1979 (*1–3*). Because of this dramatic decline, SLE belugas received the status of endangered species from the Canadian government in 1980 (*3*). Yet no solid data indicate population recovery. To explain this apparent failure to recover, we initiated a study in 1982 to carry out systematic postmortem examination of dead SLE beluga that drift ashore and to determine tissue levels of chemical contaminants.

Live and dead SLE beluga are heavily contaminated by agricultural and industrial contaminants such as heavy metals, polycyclic aromatic hydrocarbons (PAHs), and polychlorinated biphenyls (PCBs), dichlorodiphenyltrichloroethane (DDT), and their metabolites(*4–8*).

In this article we present an overview of the results of necropsies conducted over 17 years (1983–1999). The rate of cancer in the SLE beluga population is higher than in any other population of wild terrestrial or aquatic animals.

Materials and Methods

The public and officials of various government agencies reported carcasses found dead stranded on the shoreline, which were transported to the postmortem room of the Faculté de Médecine Vétérinaire de l'Université de Montréal, 500 km to the southwest, where pathologists assisted by veterinary students examined them upon arrival. Samples of all organs and lesions were preserved in neutral 10% buffered formalin; fixed tissues were embedded in paraffin, sectioned 5–7 µm thick, and routinely stained with hematoxylin-phloxin-saffron. Special stains were used when needed.

We submitted all tumors to the Department of Veterinary Pathology of the Armed Forces Institute of Pathology (AFIP; Washington, DC) for archiving in the Marine Mammal Database and/or for consultation purposes.

We determined the age of 190 carcasses by counting dentine growth layers on longitudinal section of teeth, using the standard of two growth layers per year (*9*).

The standardized rate ratio of digestive system cancer in both men and women in Québec takes into account the standardized rate ratio for each health unit in Québec (*10*). This ratio represents the number of new cases of cancer diagnosed and reported in the province of Québec during the specified time period (1989–1993) divided by the expected incidence over the same period. These ratios were represented geographically using Arcview version 3.2 (ESRI, Redlands, CA).

The Centre Hospitalier Universitaire de Québec provided all the human cancer epidemiologic data.

Results

Mortality. The study was initiated in September 1982, but in this review we include only complete years between 1983 and 1999. During this time period, 263 belugas were found dead, drifting, or stranded along the SLE shoreline. We examined 129 carcasses in the postmortem room. Of these, we considered 100 to be reasonably well preserved (77%) based on the firm consistency of the liver. Eighty of the relatively fresh 100 belugas (80%) were adult (> 7 years old).

To interpret the data presented here, the following observations must be considered. First, 51% (134 of 263) of stranded reported animals have not been necropsied, so the

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Incidence data were provided to Health Canada from the Canadian Cancer registry at Statistics Canada. We gratefully acknowledge the cooperation of the provincial and territorial cancer registries, which supply the data to Statistics Canada. We thank S. De Guise, S. Lair, R.J. Letcher, L. Measures, and R. Norstrom for helpful discussions. We thank R. Plante and C. Guimont (Filmar) for recovering and transporting carcasses to our facility over the last 15 years, all students who helped with postmortem examinations, and our colleagues at the FMV for their consistent support.

We acknowledge the help of the Centre Océanographique de Rimouski for logistic support, and the financial support of World Wildlife Fund Canada, Alcan, Fisheries and Oceans Canada, Fondation de la Faune du Québec, Société des Parcs du Québec, and NSERC.

Received 25 May 2001; accepted 20 September 2001.

cause of death and lesions affecting these animals remain unknown. The number of animals stranded dead during winter is also unknown. In the spring, summer, and fall, carcasses with terminal diseases are often found after several days of rough weather, suggesting that the number of strandings occurring during winter is at least the same as that reported during the rest of the year, because of the harsh weather conditions prevailing in that season. Young calves (< 1 year) are difficult to find in the wild because of their small size and blue-gray color. Therefore, calf mortality is probably underestimated.

A mathematical model suggests that there are fewer live animals in the 21- to 25-year age group in the SLE population than in the northwest Alaska (NA) population (*11*,*12*). Yet stranded dead SLE beluga in that age group died in higher numbers; SLE beluga stranded dead had a mortality peak between 21 and 25 years (Figure 2) (*13*). In NA beluga, the estimated age-specific death rate per age class is highest in the 0–5 year group, decreases abruptly in the 6–10 year age group, and then decreases slowly until maximum life span (38 years). Thus, the age structure of SLE beluga dying of natural causes appears clearly different from that of NA beluga, principally because most SLE belugas die at an earlier age (between 21 and 25 years old).

Primary causes of death and types of cancer. Overall, the three primary causes of death of SLE beluga were metazoan parasites (22%), cancer (18%), and infectious agents (bacterial, viral, or protozoan, 17%) (Figure 3). The major cause of death in adult beluga (n = 79) was cancer. We found 21 cancers in the 100 well-preserved carcasses examined, and of these, excluding the ovarian tumors, 18 were terminal (cancers that led to death).

Thirty percent (6 of 21) of the cancers affecting SLE beluga originated from the intestine close to the stomach, whereas a seventh intestinal cancer was closer to the anus (*14*). All other cancers are listed in Table 1.

Cancer epidemiology in SLE beluga. The annual rate of cancer in the SLE beluga population was estimated as the number of new cases of cancers per year. The estimated annual rate (AR) was calculated, as in Dorn et al. (*15*), as an annual rate per 100,000 animals. The actual number of stranded SLE beluga with cancer that were examined in the necropsy room was divided by 17 years (1983–1999) and by the estimated number of SLE beluga, and the result was multiplied by 100,000 animals. A recent index estimate of 650 SLE belugas was used (*1,16*).

$$\begin{aligned} \mathrm{AR} &= \frac{\text{SLB with cancer}}{t} \\ &\times \frac{100{,}000\ \text{SLB}}{\text{Estimated current population}} \\ &= \frac{18\ \text{SLB}}{17\ \text{years}} \times \frac{100{,}000\ \text{SLB}}{650\ \text{SLB}} \\ &= 163\ \text{SLB with cancer per year}, \end{aligned} \quad [1]$$

where AR is the estimated annual rate of cancer in SLE beluga, SLB is the beluga inhabiting the SLE, and t is the study period (1983–1999).

Stranded carcasses are rarely reported in winter (January–March) because of the ice cover, difficult access to most of the shoreline, inclement weather, and the presence of few human observers on the shoreline. To estimate the number of dead animals that strand over a complete year, we assumed that the frequency of death during the winter months is equal to that of other seasons (although it is probably higher for the above reasons), so we used a correction factor of 12 months/9 months (1.33). Assuming that all carcasses have an equal chance of being seen and collected whatever the cause of death, we estimated the minimum number of SLE beluga with cancer (estimated minimum with cancer, EMC) over the last 17 years (1983–1999) as follows:

$$\begin{aligned} \mathrm{EMC} &= \frac{\text{SLB with cancer}}{100\ \text{SLB}} \times \text{dead SLB} \times 1.33 \\ &= \frac{18\ \text{SLB}}{100\ \text{SLB}} \times 263\ \text{dead SLB} \times 1.33 \\ &= 63\ \text{with cancer}, \end{aligned} \quad [2]$$

where EMC is the estimated minimum number of SLE beluga with cancer per year, and Dead SLB is the total number of beluga reported dead and/or examined during the study period (1993–1999). The adjusted estimated annual rate (AAR) of cancer for a complete year (12 months) is:

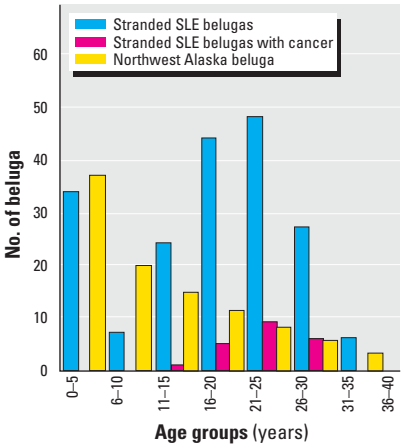

Figure 2. Age structure of SLE beluga found dead on the shoreline (1983–1997) compared with that of NA beluga obtained through subsistence hunting. We took the data for NA beluga from Alaska Department of Fish and Game's (*13*) Table 7 (model population of 1,000 beluga), from the column labeled number of deaths per 1,000 beluga. We divided the latter figures by 10 to obtain a model population of 100 beluga.

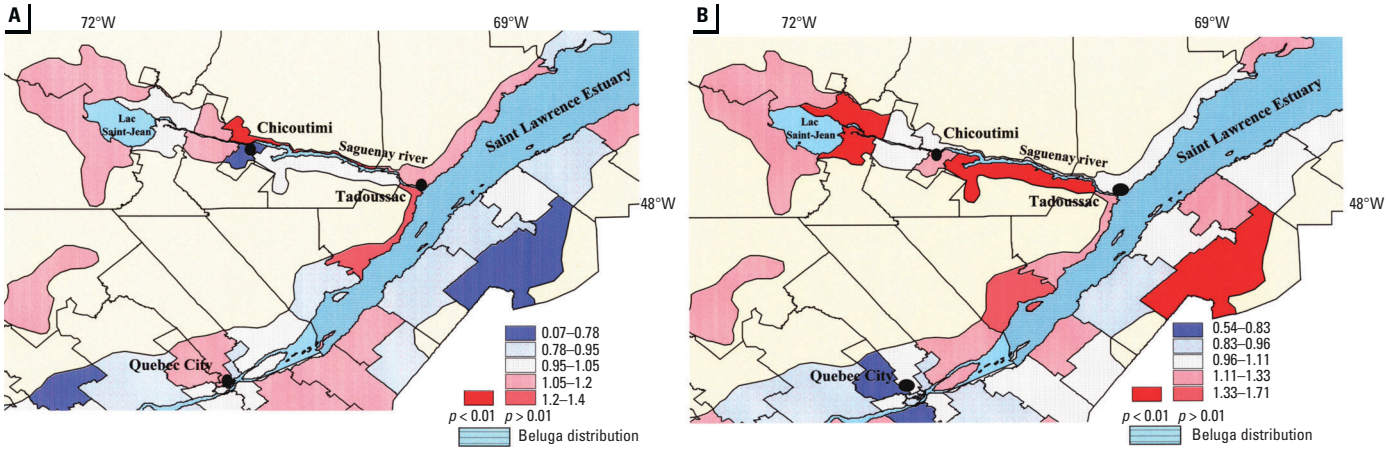

Figure 1. Distribution of beluga in the SLE and incidence of standardized rate ratio for digestive system cancer in (*A*) men and (*B*) women in Québec.

$$\text{AAR} = \frac{\text{EMC}}{t} \times \frac{100{,}000\ \text{SLB}}{650\ \text{SLB}}$$
$$= 63 \times \frac{100{,}000\ \text{SLB}}{650\ \text{SLB} \times 17\ \text{years}}$$
$$= 570\ \text{SLB with cancer}, \quad [3]$$

where SLB is the beluga inhabiting the SLE and t is the study period (1993–1999).

Discussion

Sample representativeness. This study has been carried out well over a decade. Considering the beluga life span (35–40 years), a sizable proportion of the population died and has been examined over this period. Except for young calves (< 1 year) and for the winter season, it is assumed that all carcasses have equal chances of being recovered and examined whatever the cause of death, for the following reasons: These whales live in a restricted range, as shown by thorough surveys from airplanes and boats (*1,17,18*); all carcasses have been found within that range or downstream, as a result of drift; and we used no criteria other than reasonable preservation and carcass accessibility to determine whether a given carcass would be examined in the postmortem room. In conclusion, although some deaths may occasionally escape our attention, the sampling of carcasses is most likely representative of the population in terms of causes of mortality.

Comparison of SLE beluga whales with other cetaceans. Cancers in stranded SLE beluga are more numerous than in other cetaceans, where cancer is a rare event and where major causes of death are, excluding recent viral epizootics, entanglement in fishing gear, pneumonia and/or parasitism, and abandonment and starvation of neonates (*19–21*).

No tumors were observed in 19 carcasses of other species of marine mammals living in the SLE and examined by a veterinary pathologist during the same period, using the same postmortem examination protocol (*22*). Only 33 cases of cancer have been reported worldwide in captive and wild cetaceans other than SLE beluga (Tables 1–3).

The types of cancer seen in SLE beluga also differ widely from those seen in other cetaceans (Tables 2 and 3). Gastrointestinal epithelial cancers were the most frequent cancers seen in SLE beluga; in contrast, hemopoietic cancers are the most frequent types of cancer observed in other cetaceans (Tables 1–3). Only one of the 33 cancers (3%) seen in other cetaceans was a gastrointestinal epithelial cancer. Furthermore, no mammary gland cancers had been previously reported in other cetaceans, whereas three of these cancers have been reported in SLE beluga (*23*).

A single cancer was found in over 1,800 other cetaceans examined, and tumors were not found in approximately 50 beluga examined in the Canadian Arctic [D.J. St. Aubin, personal communication, cited in (*22*)]. Arctic data may not be fully representative, however, because the age of Arctic beluga was unknown and these were randomly selected live animals and not stranded animals that died spontaneously. A single benign tumor was observed in 55 slaughtered pilot whales in Newfoundland (*24*), and only two benign tumors (0.1%) were reported in 2,000 mysticetes (baleen whales) hunted in South Africa (*19*).

The present study can best be compared with studies on singly stranded cetaceans rather than with studies performed on cetaceans shot or caught singly or collectively in fishing gears. None of these studies have shown a cancer rate comparable to that of SLE beluga. Neoplasia was not observed in 86 small odontocetes stranded on the Oregon and California shoreline (*20,21*). Among 90 bottlenose dolphins (*Tursiops truncatus*) stranded along the Gulf coast of Texas from 1991 to 1998, two cancers (or 2%), a myelogenous leukemia and a bile duct carcinoma, were found (*25*). No cancers were found in 28 harbor porpoises stranded on the British coast (*26*). Three cancers were found during the postmortem examination of 422 odontocetes (or 0.7%) from British waters (*27*), and a retrovirus may have been the etiologic agent of five lymphomas observed in dolphins on the American East Coast (*28*).

Comparison with other species. In the Western world, cancer causes 23% of all deaths in humans, a percentage comparable

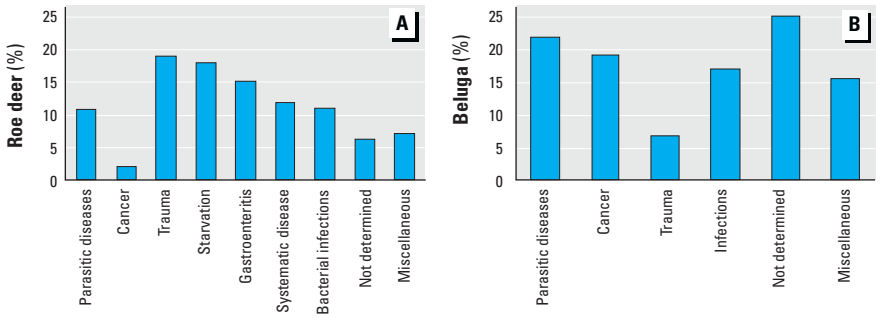

Figure 3. Primary causes of death in the SLE beluga (*B*) between 1983 and 1999 compared with those of roe deer (*A*) in Sweden between 1985 and 1995 (*32*).

Table 1. Cancers reported in stranded beluga from the SLE (1983–1999).

Organ	Cancer type	Identification	Age (years)	Sex	Reference	AFIP accession number
Intestine	Adenocarcinoma	8907	≥ 29.5	M	(*22*)	2462295–3
Intestine	Adenocarcinoma	8908	≥ 20.5	M	(*22*)	2462247–4
Intestine	Adenocarcinoma	9302	≥ 25	M	(*14*)	2461200
Intestine	Adenocarcinoma	9402	≥ 27.5	M	(*14*)	2464226–6
Intestine	Adenocarcinoma	9407	≥ 27	F	(*11*)	2582000
Intestine	Adenocarcinoma	9605	≥ 23	F	Unpublished	2573961–6
Intestine	Adenocarcinoma	9809	≥ 18	M	Unpublished	2732611–00
Skin	Squamous cell carcinoma	Same animal (9809)				
Stomach	Adenocarcinoma	8804	≥ 21	F	(*22*)	2456949–3
Stomach	Adenocarcinoma	9401	≥ 27.5	M	(*11*)	2508095–300
Salivary gland	Adenocarcinoma	8606	≥ 24.5	M	(*81*)	2457053–3
Mammary gland	Adenocarcinoma	8809	≥ 22	F	(*22*)	2456952–7
(Liver)	Poorly differentiated carcinoma, probably a metastasis[a]	Same animal (8809)				
Mammary gland	Adenocarcinoma	9804	20.5	F	(*23*)	2674669 00
Mammary gland	Adenocarcinoma	9803	≥ 26	F	(*23*)	2674861 00
Uterus	Adenocarcinoma	9502	≥ 26	F	(*82*)	2573966–5
All organs	Metastatic carcinoma	9609	≥ 23	M	Unpublished	2656322–1 00
Ovary	Granulosa cell tumor	8502	24.5	F	(*5*)	2519612
Ovary	Granulosa cell tumor	8813	≥ 21	F	(*22*)	2462292–0
Ovary	Dysgerminoma[b]	8906	≥ 25	F	(*22*)	2462229–2
Thymus	Lymphosarcoma	9001	≥ 18.5	M	(*22*)	2519747
Neuroendocrine	Carcinoma	9905	11	F	Unpublished	2732823–00
Urinary bladder	Transitional cell carcinoma	8318	16.5	M	(*83*)	

[a]Was originally classified as a primary liver cancer [beluga no. 5 in Kingsley and Hammill (*18*)]; reclassified as metastasis after consultation with AFIP. [b]Was originally classified as Granulosa cell tumor [beluga no. 16 in Kingsley and Hammill (*18*)]; reclassified as dysgerminoma after consultation with AFIP.

to that seen in SLE beluga (*29*). In wild animal populations, cancer has not been reported as a major cause of mortality in adults, with the possible exception of virus-induced liver cancer in woodchuck and retrovirus-induced leukemia in rodents (*30,31*). Instead, trauma and starvation are among the most frequent causes of death (Figure 3) (*32*). Both viruses and carcinogenic contaminants have been suspected to cause a high prevalence of metastatic carcinomas in California sea lions (*33*).

In veterinary and human epidemiology, the number of individuals at risk must be known precisely in order to determine disease prevalence. This requirement explains why few epidemiologic cancer studies have been carried out in wild mammal populations, which are notoriously ill defined and/or widespread. SLE belugas are an exception in this regard. This population is reasonably well characterized, geographically isolated, and restricted to a relatively small area and has been the object of numerous censuses often carried out using different techniques (*1,17,18*). All censuses have provided similar results, so the population at risk—the denominator used to calculate the AR (*15*)—is reasonably well defined.

We compared the AR and the AAR with those of domestic animals and humans (Figure 4). The AR of cancer, of epithelial cancer of the proximal intestine, of gastric cancer, of gastrointestinal epithelial cancer, and of mammary cancer was generally higher in SLE beluga than in domestic animals seen in veterinary hospitals. For all types of cancer, with the exception of mammary gland cancer, the SLE beluga AAR was higher than that in all other animal species and in humans. The AAR of mammary gland cancer was the same as the rate seen in humans and was comparable to the rate seen in dogs examined in veterinary hospitals (Figure 4).

Paradoxically, the collection of epidemiologic data from the SLE population resembles more closely that of humans than that of domestic animals because the denominator

Table 2. Cancers reported in cetaceans other than SLE beluga.

Species (no.)	Organ	Cancer	Age	Sex	Sources	Reference
Bottlenose dolphin	Liver, lungs	Reticuloendotheliosis	U	F	U	Ridgway, pers. comm. in (*84*)
Bottlenose dolphin (3)	Multisystemic	Immunoblastic malignant lymphoma	Adults	F	Florida	(*28*)
Atlantic spotted dolphin (1)	Multisystemic	Immunoblastic malignant lymphoma	Adult	F	Florida	
Pantropical spotted dolphin (1)	Multisystemic	Immunoblastic malignant lymphoma	Adult	F	Florida	
Bottlenose dolphin	Blood	Myelogenous leukemia	Adult	F	Gulf coast of Texas	(*25*)
Bottlenose dolphin	Liver	Cholangiocarcinoma	Adult		Gulf coast of Texas	(*85*)
Bottlenose dolphin	Spleen, lymph nodes	Lymphosarcoma	Adult	F	U	Taylor and Greenwood, pers. comm. in (*84*)
Pacific white-sided dolphin	Spleen, lymph nodes	Lymphosarcoma	Adult	M	U	(*21*)
Pacific white-sided dolphin	Spleen, lymph nodes, liver, kidney	Eosinophilic leukemia	Adult	M	U	(*21*)
Bottlenose dolphin	Pancreas	Carcinoma	Adult	M	U	Taylor and Greenwood, pers. comm. in (*84*)
Pilot whale	Ovary	Granulosa cell tumor	Adult	F	U	(*86*)
Harbor porpoise	Unknown	Adenocarcinoma		F	British waters	(*87*)
Harbor porpoise	Stomach	Adenocarcinoma	Adult	F	Northern Wadden Sea	(*88*)
Amazon River dolphin	Lung	Squamous cell carcinoma	Adult	F	U	(*65*)
Blue whale	Ovary	Granulosa cell tumor	Adult	F	Antarctic	(*89*)
Fin whale	Ovary	Granulosa cell tumor	Adult	F	Antarctic	(*89*)
Fin whale	Ovary	Granulosa cell tumor	Adult	F	Antarctic	(*89*)
Fin whale	Ovary	Carcinoma[a]	Adult	F	Antarctic	(*90*)

Abbreviations: F, female; M, male; pers. comm., personal communication; U, unknown.
[a]Reclassified as granulosa cell tumor in Geraci et al. (*65*).

Table 3. Cetaceans affected by cancer listed in the Marine Mammal Database, AFIP (updated April 2001).

Species	Status	Organ	Cancer type	Age	Sex	Sources	Percent (*n*)[a]	Accession number
Beluga	Captive	Brain	Carcinoma	19 years	M	Arctic	1.7 (56)	2034441
Bottlenose dolphin	Wild	U	Tubulopapillary adenocarcinoma	Adult	M	Gulf of Mexico	0.5 (790)	2304654
Bottlenose dolphin	Wild	Kidney	Renal cell carcinoma	Adult	F	Atlantic Ocean (South Carolina)	0.5 (790)	2445679
Bottlenose dolphin	Wild	U	Metastatic adenocarcinoma of unknown origin	U	F	Florida	0.5 (790)	2668101
Bottlenose dolphin	Wild	Multiple organs	Malignant seminoma	Adult	M	Atlantic Ocean (North Carolina)	0.5 (790)	2660824
Common dolphin (*D. delphis*)	Wild	Multiple organs	Anaplastic carcinoma (primary site undetermined)	Adult	M	California coast	2.6 (77)	2529715
Common dolphin (*D. delphis*)	Wild	Multiple organs	Solid carcinoma (primary site undermined)	Adult	M	New Jersey coast	2.6 (77)	2582000
Fin whale	Wild	Kidney	Lymphosarcoma	Adult	F	U	1.5 (8)	1470245
Killer whale	Captive	Liver, lymph node, spleen	Reticuloendotheliosis	Adult	F	U	6.2 (32)	1626236
Killer whale	Captive	Lymph node	Hodgkin disease-like (*91*)	Adult	M	Iceland	6.2 (32)	2337420
Pygmy sperm whale	U	Liver	Cholangiocarcinoma	U	U	U	0.9 (110)	1777514
Spotted dolphin (*Stenella frontalis*)	Wild	Testis, lymph nodes, adrenal glands	Malignant seminoma, pheochromocytoma	Adult	M	Gulf of Mexico	6.8 (30)	2428264
Spotted dolphin (*S. frontalis*)	Wild	Multiple organs	Malignant lymphoma	1 year	F	Gulf of Mexico	6.8 (30)	2660824

Abbreviations: F, female; M, male; U, unknown. AFIP others: brain (1 animal), kidney (1), testis and adrenals (1), ND (3).
[a](Number of animals affected by cancers of a given species) ÷ (the total number of animals for a given species examined and listed in the Marine Mammal Database of the AFIP) × 100.

used in human studies, like that used in SLE beluga, is derived from periodic census;-in contrast, the data obtained from domestic animals originates from veterinary hospitals. Because the latter population comprises many (if not mostly) sick animals, the epidemiologic data from it are expected to contain a higher rate of animals with cancer than those of the general population of domestic animals (*34,35*).

In addition, free-ranging animals generally have a shorter life span than do domestic animals because of predation (including hunting by humans), harsh environmental conditions, and malnutrition. Older animals are more numerous in the pet animal population than in free-ranging animals because of the absence of adverse conditions and because of curative and preventive improvements in veterinary medicine (*15*). Because the risk of developing cancer increases with age, cancer rates in pet, zoo, and aquarium animals are expected to be higher than in free-ranging mammals (*36*).

Considered together, these observations indicate that cancer rates in domestic animals as shown in Figure 4 are overestimated. Yet for all cancer types, the AAR in SLE beluga is much higher than that observed in cattle, horse, and sheep examined in veterinary hospitals, higher than the rate observed in dogs and cats examined in veterinary hospitals, and higher than the rate in humans.

Possible etiologic factors. Cancer of the proximal intestine is rare in all animal species and in humans. It is frequent, however, in certain bovine and ovine populations in certain parts of the world where it has been etiologically associated with the ingestion of herbicides such as 2,4-dichlorophenoxyacetic acid (*37–40*).

In cattle, small intestinal cancers result from an interaction between exogenous carcinogens and viruses. Bovine papillomavirus type 4 causes papillomas in the bovine upper digestive tract. In cattle infected with that virus and fed with bracken fern (which contains powerful carcinogens), papillomas become malignant and are accompanied by intestinal adenomas and adenocarcinomas (*37*). A similar interplay between a virus and environmental carcinogenic compounds may be at work in SLE beluga, because gastric papillomatosis has been observed in a significant number of carcasses, and particles consistent with papillomaviruses have been observed in papillomas (*5,41*).

Carcinogens are present in the environment of SLE beluga and are likely ingested by these animals. The tissue benzo[*a*]pyrene concentrations of blue mussels were 200 times higher after their transplantation into the Saguenay River than before (*42*). The sediments of the Saguenay River, which is a part of the SLE beluga habitat, contain 500–4,500 ppb of total PAH (dry weight), a concentration level significantly higher than within Osaka harbor, where PAH concentrations are 2,870 ppb, and these compounds originate from aluminum smelters located upstream (Figure 5) (*43*).

Belugas dig into sediments (*44*), and in the SLE they feed on significant amounts of bottom invertebrates (*45*). Invertebrates living in sediments contaminated by PAHs accumulate these compounds, in contrast to vertebrates (*46*). Probably because of this diet and this feeding behavior, benzo[*a*]pyrene DNA adducts have been detected in stranded SLE beluga tissue by acid hydrolysis of DNA followed by high-performance liquid chromatography (HPLC) and fluorescence detection, whereas they have not been detected in Arctic beluga tissue, which live in a presumably less contaminated environment (*5,47*). However, no differences between the two populations were observed in another study where livers were analyzed by ^{32}P postlabeling (*48*). These apparently conflicting results are not surprising given that ^{32}P postlabeling is highly sensitive for the detection of a variety of bulky DNA adducts but does not allow the precise identification of these compounds. In contrast, acid hydrolysis of DNA followed by HPLC and fluorescence detection allows the specific quantitation of benzo[*a*]pyrene diolepoxide, the ultimate carcinogenic form of benzo[*a*]pyrene. Considered together, these observations suggest that SLE beluga ingest PAHs present in benthic invertebrates, which may contribute to the elevated rate of digestive tract cancers seen in this population (*5,22,49*).

A causal relationship between intestinal adenocarcinoma and PAHs is further supported by the observation that in mice, chronic ingestion of coal tar mixtures (which contains benzo[*a*]pyrene) causes small

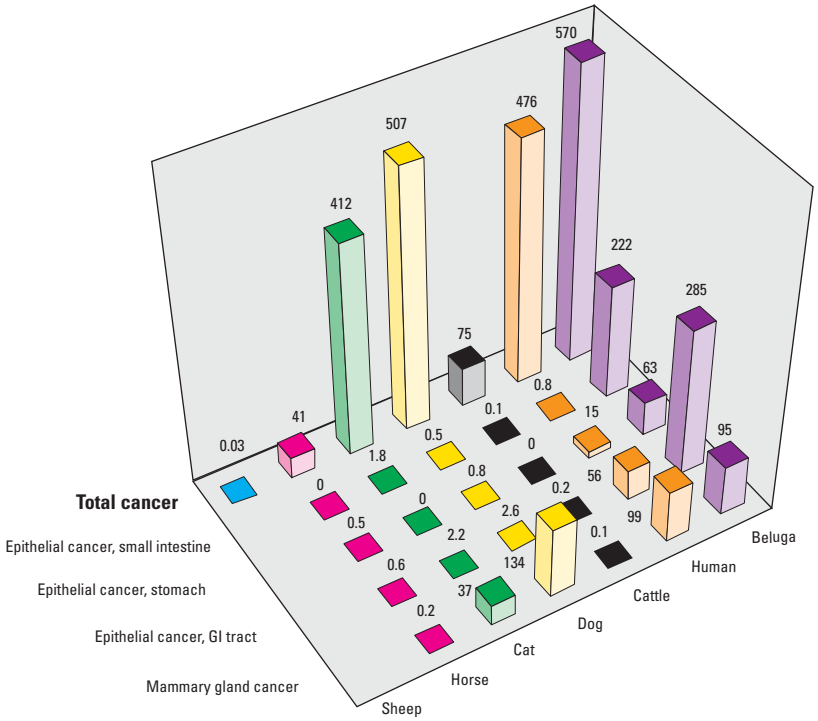

Figure 4. Adjusted annual rate (cases per 100,000) of cancer in the SLE beluga compared with that of humans and domestic animals (*34,35,92–94*).

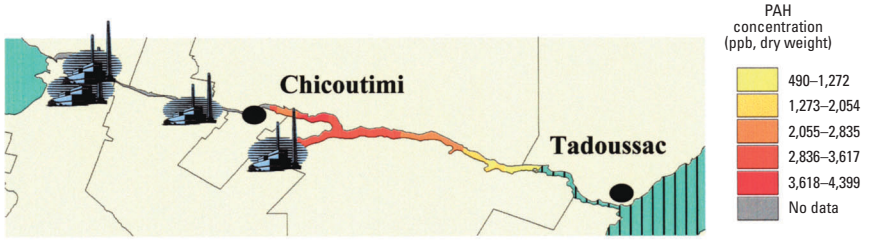

Figure 5. Saguenay River, Québec, Canada. Polycyclic aromatic hydrocarbon concentration in sediments (parts per billion, dry weight) (*43*). Chimney icon: aluminum smelters.

intestinal adenocarcinoma, forestomach papilloma, and gastric carcinoma (*50*). In humans, the ingestion of smoked food (which contains benzo[*a*]pyrene) and cancer of the small intestine have been etiologically related (*51*).

Cytochrome P450 (CYP) present in the small intestinal epithelium is among the first and among the major enzyme molecules implicated in the biotransformation and subsequent detoxication or toxification of ingested xenobiotics, and high levels of intestinal CYP have been related with gastrointestinal cancer (*52*). In the rat small intestine, the highest CYP concentrations occur in the duodenum, and the most abundant CYP is CYP1A1, known to activate PAHs into carcinogenic metabolites. It is the most abundant inducible form, and its inducibility decreases dramatically from the duodenum to the ileum (*53,54*).

Cetaceans have high levels of CYP1A and low levels of CYP2B. Compared with Arctic beluga, SLE belugas have elevated levels of both types of enzymes, probably because CYP are induced by exposure to high levels of PCBs [reviewed by Muir et al. (*7*)]. Considered together, the above observations suggest that intestinal CYP1A levels are elevated in SLE beluga and that these high levels may trigger the development of intestinal cancer by activating ingested PAHs into carcinogenic compounds. Besides inducing CYP enzymes, PCBs are also known immunosuppressive compounds. The possibility that PCB-induced diminished immunosurveillance contributes to cancer etiology has been discussed elsewhere (*55*).

A relation between ingestion of carcinogens and cancer in wildlife is not without precedent. In bottom-dwelling fish, labial papilloma and liver cancer are strongly associated with chemical contamination of sediments (*56*). Lake whitefish (LWF) are the only salmonids feeding on benthic fauna. Tissue concentrations of organochlorine compounds (OC) and of heavy metals found in LWF living in the SLE are three to five times higher than those of sympatric fish species (including nonsalmonid bottom-dwelling species), and these high concentrations coincide with a high prevalence of liver cancer in LWF (*57,58*). Thus, beluga and LWF, two aquatic vertebrate species that widely diverge taxonomically, may both be affected by cancer because both feed on the bottom, an unusual feature within their respective taxonomic group.

Mammary gland cancers were the cause of death of three (7.7%) of the adult female beluga examined from 1983 to 1999 (*23*). Mammary gland cancers have not been reported in other marine mammals and are rare in herbivores, including cattle, which are phylogenetically close to cetaceans; only isolated cases have been reported in other free-ranging wildlife species (*59,60*). In contrast, these tumors are common in humans, domestic carnivores, and rodents. These cancers have been etiologically related with viruses only in rodents [although retroviral sequences have recently been found in human cancerous breast (*61*)]. In women, these cancers have been related etiologically with OCs and PAHs (*62–64*). Alternatively, or concurrently with OCs and PAHs, these tumors may develop because of the extended hormonal stimulation associated with the long pregnancy and lactation of cetaceans (*65*).

In the Saguenay–Lac Saint-Jean region, aluminum workers are affected by a high prevalence of lung and urinary bladder cancer. These cancers have been epidemiologically related with exposure to coal tar volatile components produced by the combustion of carbon anodes used for the electrolysis of aluminum (*66,67*). Elsewhere, gastric cancers have been also epidemiologically related with working in aluminum plants where carbon anodes are prebaked (*68*).

The incidence of cancer of the stomach, digestive tract, and breast is also higher in the Saguenay population that does not work in the aluminum industry (*10*) (Figures 1 and 5). This high cancer incidence could be related to the fact that the drinking water of 79% of the population comes from local surface water (rivers and lakes) and that large quantities of PAHs have been, and are, released locally into the atmosphere by local aluminum smelters (*69,70*). Because of cheap hydroelectricity and accessibility to the sea, aluminum smelters have been in operation in that region since as early as 1926. Between 1937 and 1980, 40,000 tons of PAHs generated by the aluminum smelters have accumulated in the fjord watershed, from which 20 tons are released per year and from which 3% are benzo[*a*]pyrene, a strong carcinogen (*71*). Both the magnitude and the persistence of this threat to public health have been clearly recognized (*71*).

Together, these observations suggest that a human population and a population of long-lived, highly evolved mammals may be affected by specific types of cancer because they share the same habitat and are exposed to the same environmental contaminants.

In people, genetic susceptibility to cancer takes two forms: hereditary cancer syndromes (HCSs) such as familial adenomatous polyposis, and population susceptibility, where an ensemble of individuals has an increased risk of cancer (but not as high as in HCSs). Because inbreeding has led to some degree of genetic homogeneity in SLE beluga, the possibility of an HCS within the SLE beluga population has to be considered (*72*). HCSs affect multiple—and most often young—members of a same family (*73,74*). Beluga with cancer were not younger than beluga dead of other causes (Table 1, Figure 2). In addition, other genetically homogeneous free-ranging or captive wildlife populations have not been found affected by high rates of cancer (*75,76*). An apparent exception is the highly inbred black-footed ferret (*Mustela nigripes*), where a high prevalence of cancers has been observed. However, all black-footed ferrets affected by cancer have been kept in captivity. Captivity greatly extends the life span of these animals, from 4 years in the wild to 7–9 years in captivity. Because all tumors develop only in ferrets older than 5 years, captivity clearly plays a major role in the etiology of these tumors by extending life span (*77*). In addition, these animals may have been exposed to carcinogenic compounds in captivity. Thus, there is no evidence supporting that cancer in SLE beluga is a hereditary cancer syndrome.

In population susceptibility to cancer, an ensemble of individuals has increased risk of developing cancer because these individuals have a specific and common genetic feature caused by normal polymorphism (*73*). This feature most often influences the metabolism of carcinogenic xenobiotics. It can be envisaged that some SLE beluga have highly induced CYP1A1 in the proximal intestinal epithelium, rendering cells susceptible to mutagenesis by DNA-damaging metabolites generated from specific xenobiotics such as benzo[*a*]pyrene.

There is no evidence that cancer is frequent in beluga as a species. A single case of cancer is listed among the 56 belugas listed in the Marine Mammal Database (Table 3). The few significantly prevalent cancers observed in wild mammals have a viral etiology.

Two lines of evidence are not consistent with the high rate of cancer being caused by old age. First, SLE beluga affected with cancer did not reach the maximum life span reached by Arctic beluga; and second, SLE beluga with cancer showed the same age distribution as did beluga dead of other causes (Figure 2).

Future studies. Few odontocetes species feed on benthic invertebrates: the Amazon river dolphin (*Inia geoffrensis*), the Franciscana (*Phocoena blainvillei*), the Susu (*P. gangetica*), and the Irrawaddy dolphin (*Orcinus brevirostris*) (*78*). Because these species generally inhabit rivers that are often more contaminated than the open ocean, high rates of cancers of the gastrointestinal tract may also be found in these species.

Several chemical carcinogens leave a signature on the host genome by causing mutations at specific sites in genes involved in cell proliferation, such as p53 and *ras*. The finding

of the same signature in tumors of SLE beluga, fish, and humans would strongly support the etiologic role of contaminants in carcinogenesis (*79,80*).

Because cancer is an ultimate but rare consequence of chemical mutagenesis, the epidemiologic association of xenobiotics with carcinogenesis requires the examination of large numbers of animals. To demonstrate the role of xenobiotics in carcinogenesis in SLE beluga, convincing statistics would require much larger numbers of whales and/or the follow-up of SLE beluga for many more decades. The observation of high prevalences of cancer in other populations of marine mammals similarly exposed to carcinogens would strengthen an etiologic relationship with chemical carcinogenesis.

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