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

Sylvain De Guise,1,2 Daniel Martineau,3 Pierre Béland,2 and Michel Fournier1

1TOXEN, Université du Québec à Montréal, Montréal, Québec; 2St. Lawrence National Institute of Ecotoxicology, Montréal, Québec; 3Faculté de Médecine Vétérinaire, Université de Montréal, St-Hyacinthe Québec, Canada

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)

Key words: PCBs, organohalogens, beluga whales, cetaceans, reproduction, endocrinology, immunology, tumors

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...
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 corpuscles on serial sections of ovaries demonstrated little ongoing ovarian activity compared to what is reported in Arctic belugas (21,22). An adult hermaphroditic 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 gray 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 adrenocorticotrophic 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 adrenocorticotrophic 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 cytoxic 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 thymus-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 policed 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 seminfield 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 papillomavirus (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.

Throughout 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.
REFERENCES

1. Reeves RR, Mitchell E. Catch history and initial population of white whales (Delphinapterus leucas) in the river and gulf of St. Lawrence. Can Canad J Fisheries and Oceans Canada. Nat Can (Rev Ecol Syst) 11:63–121 (1984).

2. Michaud R. Survols aériens pour l’estimation de la distribution saisonnière et des déplacements des bélugas. Montréal: Rapp Inst Natl Écotoxicol St-Laur, 1990.

3. Pippard L. Status of the St. Lawrence River population of beluga whales (Delphinapterus leucas). Can Field Nat 99:438–450 (1985).

4. Martinneau D, Béland P, Desjardins C, Lagacé A. Levels of organochlorine chemicals in tissues of beluga whales (Delphinapterus leucas) from the St. Lawrence Estuary, Québec, Canada. Arch Environ Contam Toxicol 16:137–147 (1987).

5. Martinneau D, Lagacé A, Béland P, Higgins R, Armstrong D, Shugart W. Pathology of stranded beluga whales (Delphinapterus leucas) from the St. Lawrence estuary, Québec, Canada. J Comp Pathol 98:287–311 (1988).

6. Muir DCG, Ford CA, Stewart REA, Smith TG, Addison RF, Zinck ME, Béland P. Organochlorine contaminants in belugas, Delphinapterus leucas, from Canadian waters. Can Bull Fish Aquat Sci 224:165–190 (1990).

7. Wagemann R, Stewart REA, Béland P, Desjardins C. Heavy metals and selenium in tissues of beluga whales, Delphinapterus leucas, from the Canadian Arctic and the St. Lawrence estuary. Can Bull Fish Aquat Sci 224:191–206 (1990).

8. De Guise S, Lagacé A, Béland P. Tumors in St. Lawrence beluga whales (Delphinapterus leucas). Vet Pathol 31:444–449 (1994).

9. De Guise S, Lagacé A, Béland P, Girard C, Higgins R. Non-neoplastic lesions in beluga whales (Delphinapterus leucas) and other marine mammals from the St. Lawrence Estuary. J Comp Pathol (in press).

10. Colborn T, vom Saal FS, Soto AM. Developmental effects of endocrine-disrupting chemicals in wildlife and humans. Environ Health Perspect 101:378–384 (1993).

11. Reijnders PHJ. Organochlorine and heavy metal residues in harbour seals from the Wadden Sea and their possible effects on reproduction. Neth J Sea Res 14:30–65 (1980).

12. Baker JR. Pollution-associated uterine lesions in grey seals from the Liverpool Bay of the Irish Sea. Vet Rec 125:303 (1989).

13. Helle E, Olsson M, Jensen S. DDT and PCB levels and reproduction in ringed seals from the Bothnian Bay. Ambio 5:188–189 (1976).

14. Helle E, Olsson M, Jensen S. PCB levels correlated with pathological changes in seal uteri. Ambio 5:135–137 (1976).

15. DeLong RL, Gilman RG, Simpson JG. Premature births in California sea lions: association with high organochlorine pollutant residue levels. Science 181:1168–1169 (1973).

16. Subramanian A, Tanabe S, Tatsukawa R, Saito S, Miyazaki N. Reduction in the testosterone levels by PCBs and DDE in Dall's porpoises of the northwestern North Pacific. Mar Pollut Bull 18:643–646 (1987).

17. Sharpe RM, Skakkebaek NE. Are oestrogens involved in the falling sperm count and disorders of the male reproductive tract? Lancet 341:1392–1395 (1993).

18. Reijnders PHJ. Reproductive failure in common seals feeding on fish from polluted coastal waters. Nature 324:456–457 (1986).

19. Béland P, Vézina A, Martinneau D. Potential for growth of the St. Lawrence (Québec, Canada) beluga whale (Delphinapterus leucas) population based on modelling. J Cons Int Explor Mer 45:22–32 (1988).

20. Bush B, Bennett A, Snow J. Polychlorobiphenyl congeners, p,p'-DDE, and sperm function in humans. Arch Environ Contam Toxicol 15:333–341 (1986).

21. Burns JJ, Seaman GA. Investigations of belukha whales in coastal waters of western and northern Alaska. I. Biology and ecology. Report No. NA 81 RAC 0049. Fairbanks: Alaska Dept Fish and Game, 1985.

22. De Guise S, Béland P. Étude histologique de coupes sérieuses d’ovaires de bélugas (Delphinapterus leucas) du Saint-Laurent. Rev Ecol Biol Anim 28:79–88 (1988).

23. De Guise S, Lagacé A, Béland P. True hermaphroditism in a St. Lawrence beluga whale (Delphinapterus leucas). J Wildl Dis 30:287–290 (1994).

24. Byrne JE, Carbone JP, Hanson E. Hypothyroidism and abnormalities on the kinetics of thyroid hormone metabolism in rats treated chronically with polychlorinated biphenyls and polychlorinated biphenyls. Endocrinology 121:520–527 (1987).

25. Collins WT, Capen CC, Kasza L, Carter C, Dailey RE. Effects of polychlorinated biphenyls (PCB) on the thyroid gland of rats. Am J Pathol 89:119–136 (1977).

26. Schumacher U, Zahler S, Horny H-P, Heidemann G, Skirniss K, Welsch U. Histological investigations on the thyroid glands of marine mammals (Phoca vitulina, Phocaena phocoena) and the possible implications of marine pollution. J Wildl Dis 29:103–108 (1993).

27. Brouwer A, Reijnders PHI, Koeman JH. Polychlorinated biphenyl (PCB)-contaminated fish induces vitamin A and thyroid hormone deficiency in the common seal (Phoca vitulina). Aquat Toxicol 15:99–106 (1989).

28. St. Aubin DJ, Geraci JR. Seasonal variation in thyroid morphology and secretion in the white whale, Delphinapterus leucas. Can J Zool 67:263–267 (1989).

29. Bergman A, Olsson M. Pathology of Baltic grey seal (Halichoerus grypus) and ringed seal (Pusa hispida) females with special reference to adrenocortical hyperplasia: is environmental pollution the cause of a widely distributed disease syndrome? In: Proceedings of the Symposium on Seals in the Baltic and Eurasian Lakes, 5–8 June 1985, Savonlinna, Finland. Copenhagen: International Council for the Exploitation of the Sea, 1985;1–27.

30. Brandt I, Jönsson C-J, Lund B-O. Comparative studies on adrenocorticotropic DDT-metabolites. Ambio 21:602–605 (1992).

31. Capen CC. The endocrine glands. In: Pathology of Domestic Animals, Vol 3, 4th ed (Jubb KFV, Kennedy PC, Palmer N, eds). New York: Academic Press, 1993;267–348.

32. Brown WR, Gough A, Hamlin MH, Hottendorf GH, Patterson DR. Proliferative lesions of the adrenal glands of rats. In: Proceedings of the Society of Toxicology Pathologists, 2–6 June 1991, Monterey, California. Monterey, CA: Society of Toxicology Pathologists, 1991;1–24.

33. DeLellis RA. The endocrine system. In: Pathological Basis of Disease, 4th ed (Cotran RS, Kumar V, Robbins SL, eds). Philadelphia: WB Saunders Company, 1989;1205–1276.

34. Geraci JR, Testaverde SA, St. Aubin DJ, Loop TH. A mass stranding of the Atlantic white-sided dolphin, Lagenorhynchus acutus: a study into pathobiology and life history. Report No. MMC-75/112. Washington: Marine Mammal Commission, 1978.

35. Andersson L, Nikolaaidis E, Brunstrom B, Bergman A, Dencker L. Effects of polychlorinated biphenyls with Ah receptor affinity on lymphoid development in the thymus and the bursa of Fabricius chick embryos in ovo. Toxicol Appl Pharmacol 107:183–188 (1991).

36. Davis D, Safe S. Immunosuppressive activities of polychlorinated dibenzo-p-dioxin related halogenated hydrocarbons: examination of the
MECHANISMS OF ACTION OF CONTAMINANTS ON BELugas

mechanism of toxicity. Annu Rev Pharmacol Toxicol 22:517–554 (1982).

39. Exon JH, Takort PA, Koller LD. Effect of lead, polychlorinat-
ed biphenyls and cyclophosphamide in rat natural killer cells, interleukin 2, and antibody synthesis. Fundam Appl Toxicol 5:158–164 (1985).

40. Smialowicz RJ, Andrews JE, Riddle MM, Rodgers RR, Loebke RW, Copeland CB. Evaluation of immunotoxicity of low level PCB exposure in the rat. Toxicology 56:197–211 (1989).

41. Tryphonas H, Hayward S, O’Grady L, Loo JCK, Arnold DL, Bryce F, Zawizda Z.Z. Immuno-toxicity studies of PCB (Aroclor 1254) in the adult rhesus (Macaca mulatta) monkey — preliminary report. Int J Immunopharmacol 11:199–206 (1989).

42. Loose LD, Pittman KA, Beniz K-F, Silokworth JB. Polychlorinated biphenyl and hexachlorobenzene induced tumoral immunosuppression. J Reticuloendothel Soc 22:253–271 (1977).

43. Thomas PT, Hinsdill RD. Effect of polychlorinated biphenyls on the immune response of rhesus monkeys and mice. Toxicol Appl Pharmacol 44:41–51 (1978).

44. Loose LD, Pittman KA, Beniz K-F, Silokworth JB, Mueller W, Coulston F. Environmental chemical-induced immune dys-
function. Ecotoxicol Environ Saf 2:173–198 (1978).

45. Shigematsu N, Nomuram Y, Ishibashi T, Yoshida M, Suesugu S, Kawatsu T, Ikeda S, Saito R, Ishimaru S, Shirakusa T, Kido M, Emori K, Toshimitsu H. Clinical and experimental studies on impairment of respiratory organs in chlorobiphenyl poisoning. Fukuoka Acta Med 62:150 (1971).

46. Durham SK, Brouwer A. 3,4,3’4’-Tetrachlorobiphenyl distribution and induced effects in the rat adrenal gland. Localization in the zona fasciculata. Lab Invest 62:232–239 (1990).

47. Wasserman D, Wasserman M, Cucos S, Djavaherian M. Function of adrenal gland zona fasciculata in rats receiving polychlorinated biphenyls. Environ Res 6:334–338 (1973).

48. Cha I, Villeneuve DC, Secours V, Valli VE. Toxicological assessment of chlorinated diphenyl ethers in the rat. J Environ Sci Health 25:225–241 (1990).

49. Koller LD, Thigpen JE. Biphenyl-exposed rabbits. Ann J Vet Res 34:1605–1606 (1973).

50. Imanishi J, Nomura H, Matsubara M, Kita M, Won S-J, Mizutani T, Koshida T. Effect of polychlorinated biphenyl on viral infections in mice. Infect Immun 29:275–277 (1980).

51. Friend M, Trainer DO. Polychlorinated biphenyl: interaction with duck hepatitis virus. Science 170:1314–1316 (1970).

52. White KL, Lysy H, McCoy JA, Anderson AC. Modulation of serum complement levels following exposure to polychlorinated dibenzo-p-dioxins. Toxicol Appl Pharmacol 84:209–219 (1986).

53. Fournier M, Bernier J, Filpo D, Krzyzyniak K. Evaluation of pesticide effects on humoral response to sheep erythrocytes and mouse hepatitis virus 3 by immunosorbent analysis. Pest Biochem Physiol 26:353–364 (1986).

54. Krzyzyniak K, Hugo P, Filpo D, Fournier M. Increased sus-
cceptibility to mouse hepatitis virus 3 of peritoneal macrophages exposed to dieldrin. Toxicol Appl Pharmacol 80:397–408 (1985).

55. Krzyzyniak K, Filpo D, Mansour S, Fournier M. Suppression of avidin processing by mouse macrophage after sublethal exposure to dieldrin. Immunopharmacology 18:157–166 (1989).

56. Krzyzyniak K, Bernier J, Hugo P, Fournier M. Suppression of MTHV3 virus-activated macrophages by dieldrin. Biochem Pharmacol 35:2577–2586 (1986).

57. Bernier J, Hugo P, Krzyzyniak K, Fournier M. Suppression of humoral immunity in inbred mice by dieldrin. Toxicol Lett 35:231–240 (1987).

58. Hugo P, Bernier J, Krzyzyniak K, Fournier M. Transient inhibi-
tion of mixed lymphocyte reactivity by dieldrin in mice. Toxicol Lett 41:1–9 (1988).

59. Hugo P, Bernier J, Krzyzyniak K, Potworowski E, Fournier M. Abrogation of graft-versus-host reaction by dieldrin in mice. Toxicol Lett 41:11–22 (1988).

60. Bernier J, Blais Y, Lombardi P, Fournier M, Chevalier G, Krzyzyniak K. Immunotoxicity of aminocarb. I. Comparative studies of sublethal exposure to aminocarb and dieldrin in mice. Pest Biochem Physiol 30:238–250 (1988).

61. Jolicoeur P, Fournier M, Krzyzyniak K. Suppression of micro-
bicidal activity of peritoneal exudate by sublethal dieldrin exposure of outbred and inbred mice. Pest Biochem Physiol 31:203–212 (1988).

62. Krzyzyniak K, Trottier B, Jolicoeur P, Fournier M. Macrophase functional activities versus cellular parameters upon sublethal exposure in mice. Mol Toxicol 1:247–259 (1987).

63. De Swart RL, Ross PS, Vedder LJ, Timmerman HH, Heisterkamp SH, Van Looveren H, Vos JG, Reijnders PJJ, Osterhaus ADME. Impairment of immune function in harbour seals (Phoca vitulina) feeding on fish from polluted waters. Ambio 23:155–159 (1994).

64. Hileman B. Effects of organohalogenes on marine mammals to be investigated. Chem Eng News 70:23–24 (1992).

65. Stone R. Swimming against the PCB tide. Science 255:798–799 (1992).

66. De Guise S, Lagace A, Beland P. Gastric papillomas in a St. Lawrence beluga whales (Delphinapterus leucas). J Vet Diagn Invest 6:385–388 (1994).

67. Ray S, Dunn BP, Payne JF, Fancey L, Helbig R, Beland P. Aromatic DNA-carcinogen adducts in beluga whales (Delphinapterus leucas) from the Canadian arctic and the Gulf of St. Lawrence. Mar Pollut Bull 22:392–396 (1991).

68. Cotran RS, Kumar V, Robbins SL. Stenosis. In: Pathological Basis of Disease 4th ed (Cotran RS, Kumar V, Robbins SL, eds). Philadelphia:WB Saunders Company, 1989:239–305.

69. Levin W, Wood A, Chang R, Ryan D, Thomas P, Yagi H, Thakker D, Vyas K, Boyd C, Chu S-Y, Conney A, Jerina D. Oxidative metabolism of polycyclic aromatic hydrocarbons to ultimate carcinogens. Drug Metabol Rev 13:555–580 (1982).

70. Cohen SM, Purtilo DT, Ellwein LB. Pivotal role of increased cell proliferation in human carcinogenesis. Mod Pathol 4:371–382 (1991).

71. Yamasaki H, Lokko A, Tomatis L. Perinatal and multigen-
erational effect of carcinogens: possible contribution to deter-
mination of cancer susceptibility. Environ Health Perspect 98:39–43 (1992).

72. Roitt I, Brostoff J, Male D. Immunité antitumorale. In: Immunologie Fondamentale et Appliquée. (Roitt I, Brostoff J, Male D, eds). Paris:MEDSI/McGraw-Hill Healthcare Group, 1985:18.1–18.16.

73. Allison AC. Immunological surveillance of tumors. Cancer Immunol Immunother 2:151–155 (1977).

74. Birman J, Cecil HC. Estrogenic activity of DDT analogs and polychlorinated biphenyls. J Agric Food Chem 18:1108–1112 (1970).

75. Gergely P, Gonzalez-Cabello R, Jakab I, Vien CV, Bodo I. Effect of vitamin A treatment on cellular immune reactivity in patients with CLL. Acta Med Hung 45:307–311 (1988).

76. Bendich A. Carotenoids and the immune response. J Nutr 119:112–115 (1989).

77. Saeman WE, Blackman MA, Gindhart TD, Roubinian JR, Loeb JM, Talal N. 8-Estradiol reduces natural killer cells in mice. J Immunol 121:2193–2198 (1978).

78. Vos JG, Luster MI. Immune alterations. In: Halogenated Biphenyls, Terphenyls, Naphthalenes, Dibenzo-dioxins and Related Products, 2nd ed (Kimbrough RD, Jensen AA, eds). Amsterdam:Elsevier Science Publishers BV, 1989:295–322.

Volume 103, Supplement 4, May 1996 77