The Use of Traditional Foods in a Healthy Diet in Alaska:

Risks in Perspective

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RISKS IN PERSPECTIVE - POLYCHLORINATED BIPHENYLS (PCBS) AND OTHER POLYHALOGENATED DIAROMATIC HYDROCARBONS

Executive Summary

The Alaska Division of Public Health recommends the continued unrestricted consumption of traditional subsistence foods in Alaska. Traditional foods provide inexpensive and readily available nutrients, essential fatty acids, antioxidants, calories and protein and many health benefits such as protection from diabetes, cardiovascular disease, improved maternal nutrition and neonatal and infant brain development.

The presence of heavy metals and discovery of persistent, man-made chemicals in the arctic food chain generated concerns about the potential threat to the ecosystem and risk to human health. The global distribution of man-made pollutants through atmospheric transport is well documented; human exposures to them in the arctic occur primarily through the subsistence diet. Global policies to minimize the entry of anthropogenic pollutants into the environment and food chain should be pursued.

The subsistence lifestyle and diet are of great importance to the self-definition, self-determination, cultural and socio-economic, and overall health and well-being of indigenous peoples. At the Tenth International Congress on Circumpolar Health in May 1996, elders called for a balanced approach to evaluating the possible risks and weighing the benefits of subsistence foods to ensure the preservation of their cultural identify and total health and well-being. Elders also expressed that the fear associated with the contaminants may cause greater harm than the actual presence of the contaminants themselves and that health warnings regarding food consumption should only be made when there is strong evidence that the risks outweigh the benefits.

Severely limiting the consumption of traditional foods may result in harm by reducing the consumption of food that has health benefits and by increasing the consumption of foods that have potential health risks. While risk assessments may be valuable in regulating industrial emissions or in establishing site-specific clean up levels, food consumption advice should

occur within a broader public health context that includes consideration of both risks and benefits.

The Alaska Division of Public Health bases its recommendations on a thorough evaluation of existing scientific evidence about the potential risks from exposure to naturally occurring and anthropogenic heavy metals and anthropogenic persistent organic chemicals as well as consideration of the uncertainties in risk, the potential health benefits from consumption of traditional foods, the competing risks associated with other food sources, the potential medical impact of dietary and lifestyle changes on a population, and the social and economic ramifications of restricting traditional food consumption.

The goal of the Alaska Division of Public Health is to provide accurate advice based upon the best and most current scientific evidence. Ultimately our goal is to provide a clear explanation of the scientific evidence and our interpretation of that evidence so that each individual can with confidence make a wise decision about what foods he or she will eat. To achieve this goal, we are committed to participate in an ongoing effort to develop appropriate information in partnership with local communities. Improved communication will enable broader understanding of these complex scientific issues.

One of the important benefits of this project is the identification of needed future research. Many gaps in data and knowledge exist. We have exciting opportunities to improve our knowledge and answer lingering questions. By working together, we can help assure a healthy environment for future generations.

INTRODUCTION

Background

Discovery of low levels of heavy metals and persistent, man-made chemicals in the arctic food chain (Dewailly et al. 1994; Becker et al. 1995) generated concerns about the potential threat to the ecosystem and risk to human health. The global distribution of man-made pollutants through atmospheric transport is well documented; human exposures to them in the arctic occur primarily through the subsistence diet.

The subsistence lifestyle and diet are of great importance to the self-definition, self-determination, cultural and socio-economic, and overall health and well-being of indigenous peoples. At the Tenth International Congress on Circumpolar Health, elders called for a balanced approach to evaluating the possible risks and weighing the benefits of subsistence foods to ensure the preservation of their cultural identity and total health and well-being (Egede 1996; Kuptana 1996; Pungowiyi 1996). Elders also expressed that the fear associated with the contaminants may cause greater harm than the actual presence of the contaminants themselves (Pungowiyi 1996) and that health advisories regarding food consumption should only be made when there is strong evidence that the risks outweigh the benefits (Egede 1996).

Purpose of Report

This report has four primary purposes:
* to examine the presence and health implications of cadmium, methylmercury, and polyhalogenated diaromatic hydrocarbons in species traditionally harvested and consumed in Alaska;
* to examine and weigh the many health benefits associated with traditional foods in Alaska;
* to explain the rationale behind our overall public health advice that the benefits of traditional foods far outweigh the possible health risks;
* to identify gaps in knowledge and future areas of work to further our understanding of the nutritional and health benefits of traditional foods, and to better characterize and interpret the implications of trace metals and organochlorines in wildlife species traditionally harvested and consumed in Alaska.

Organization of Report

The introduction includes a brief background on wildlife traditionally harvested and consumed in Alaska, a review of dietary intake surveys conducted in Alaska, and a presentation of general dietary intake advice issued by the US Department of Agriculture and National Cancer Institute.

Benefits of traditional foods are discussed. Benefits include the socio-cultural and economic value associated with the use of traditional foods and the high costs associated with imported replacements of traditionally harvested foods in Alaska. Also, traditional foods provide nutrients which may not be adequately replaced by market foods. Some of the nutritional

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benefits provided by traditional foods and a discussion on the value of omega-3 fatty acids are reviewed.

Risks are discussed, with separate chapters on cadmium, methylmercury and PCBs. For the most part, we relied heavily upon existing published reports regarding tissue concentrations for cadmium, methyl-mercury, and PCB levels. We are aware that numerous unpublished findings exist in varying stages of analyses, report completion and dissemination (Hovda 1997). We also reviewed the current toxicologic and epidemiologic literature and existing World Health Organization (WHO) and other agency dietary intake guidelines and how they are formulated and applied. As new data emerge on tissue concentrations and on toxicologic and epidemiologic findings in the literature, this technical document will need to be updated.

Local point sources of pollution from industries and hazardous waste sites are not addressed in this report, because such local sources require site-specific evaluations. The document does not address well-known health risks from common food contaminants such as botulism or paralytic shellfish poisoning, as these topics have been addressed in publications and health consumption advisories elsewhere.

Traditional Foods Harvested and Consumed in Alaska

Traditional foods consumed in Alaska vary by geographic region, local preferences, and season. Fish has been and remains a primary food staple throughout the state. Marine mammals, shellfish, and to a lesser extent, ascidians (seasquirts), sea cucumbers and seaweed are commonly harvested in coastal areas. Game meats are harvested throughout the state, including locally available (moose, deer and ptarmigan) and migratory species (caribou). Berries and edible plants are gathered and consumed when available.

The Alaska Department of Fish and Game estimates that fish harvests represent 59% of all rural subsistence harvests in the state based upon a 1990 wild resource harvest survey (Figure 1; AKDFG, 1994). Many species of salmon (*Onchorynchus* spp.) are widely consumed, including King or Chinook (*O. tschawytsch*), Pink or Humpback (*O. gorbuscha*), Silver or Coho (*O. kisutch*), and Sockeye or Red (*O. nerka*) salmon. Other important subsistence fish species include Arctic Grayling (*Thymallus arcticus*), Herring (*Clupa harengus*), flounder (*Platichtys stellatus*), pike (*Esox lucius*), and several species of smelt, whitefish and cod (Nobmann 1989).

Several species of pinnipeds ("fin-footed" marine mammals) are consumed in subsistence communities. One commonly harvested and consumed pinniped throughout Alaska is the harbour seal (*Phoca vitulina*). The harbour seal is found from as far south as Ketchikan in the southeastern region to the far north of Point Barrow. Because it is widely available, it is an important component in the coastal Alaska Native diet. Although spring time hunts are common in certain areas, harbour seal can be hunted throughout the year. Another commonly hunted pinniped is the bearded seal (*Erignathus barbatus*) also called ugruk. It is found from Nunivak Island in the Bering Sea, north and eastward to the polar cap. The ringed seal (*Phoca hispida*), another common subsistence species, is found throughout the Beaufort,

Chukchi, and Bering Seas, ranging as far south as Bristol Bay in years of extensive ice coverage (Lentfer 1988). Ringed seals in Alaskan waters rarely haul out on land and are dependent on sea ice as a substrate for resting, whelping and molting. The Pacific walrus (*Odobenus rosmarus*) is usually hunted in the vicinity of the Bering Sea (from late April to early June) and later in the summer off of Point Barrow. Pinnipeds feed mainly upon fish and large crustaceans. Walruses have also been known to feed upon seals. In the Bering Strait region an observed increase in walrus seal predation was noted between 1978 and 1979 relative to the previous 25 years (Lowry et al. 1984). Seal predation has historically been regarded as an infrequent occurrence confined to only a small proportion (10%) of walruses, such as rogue walruses, but recent evidence suggests that seal predation may be more common than previously believed (Muir et al. 1992b). Local traditional knowledge regarding walrus predation habits could substantially improve upon the current literature.

The bowhead whale, also known as Greenland right whale (*Balaena mysticetus*), is a plankton filter-feeder found in the polar regions between Alaska and Greenland. Bowhead whales are hunted in April and May and again in September in Northern Alaska. The beluga whale (*Delphinapterus leucas*) is found in the arctic and subarctic and is hunted throughout the coastal areas of the state. Belugas feed primarily upon herring, salmon, squid, and crustaceans.

Game meats include caribou and moose, and to a lesser extent bear, deer, and small game, such as ptarmigan, duck, goose, turkey, owl, beaver and rabbit. Caribou

(*Rangifur tarandus*) are distributed throughout the state, but are most abundantly available in east-central Alaska and the western Yukon. Lichens represent the majority of the caribou diet, but grasses, mosses, willows and other plants are known to be consumed as well.

Because of the short growing season, there is no main agricultural crop. Although plants and berries are eaten, the traditional diet is largely a fish and animal-based diet. Nonetheless, roots, grasses, and berry fruits from locally available plants (e.g., wild rhubarb, fiddlehead ferns, beach glasswort, buttercup, sourdock leaves, willow leaves, mashu roots, seaweeds, cloudberries, salmon berries, blueberries, low bush mountain cranberries) are a nutritionally important component of traditional diets, providing necessary vitamins, minerals, and fiber. However, in the high arctic vegetation is extremely sparse and reliance upon an animal-based diet is even greater than in other areas of the state.

Overall in rural areas, the majority of wildlife harvests consist of fish (59%), land mammals (20%), marine mammals (14%), shellfish (2%), birds (2%), and plants (2%) (Figure 1). The relative composition of the wild food harvests, of course, varies geographically from coastal to interior regions, from high arctic to subarctic ecosystems, and from remote villages to larger villages and cities where access to commercial food items is greater than in remote areas.

Alaskan Dietary Intake Surveys

Traditional foods continue to be very important to Alaska Natives. Dietary surveys indicate, however, that traditional

diets have been supplemented by significant amounts of commercial and processed foods. In the late 1700s trade with Caucasians introduced sugar and flour. Estimated carbohydrate intake among Alaskan Eskimos and Indians prior to Western contact ranged from 2 to 11% and increased to approximately one-third of total calories by the 1960s (Heller, 1964).

In a dietary survey conducted between 1956 and 1961 in 11 southern and central Alaskan villages, 30-45% of the total daily calories was furnished by local food sources (Heller et al. 1967). In a 3-day dietary survey of residents from Wainwright and Point Hope conducted in 1971 and 1972, a wide range within and between villages in the relative importance of Native versus market foods was identified (Heller, as reported in Wei, 1973). Among 54 Wainwright residents, 43.7% had 50-100% of their total calories supplied by Native foods compared to 6.1% for 33 residents participating in the survey in Point Hope. Traditional Native foods, however, provided 50-100% of protein consumed for 79.2% of the Wainwright residents surveyed and 60.6% of the Point Hope residents surveyed. Because of factors which influence participation in surveys, these data should be interpreted with caution.

In 1987-1988, a 24-hour dietary food recall survey was conducted representing 359 people in 11 communities: Anchorage, Sitka, Kake, Dillingham, Pedro Bay, Pilot Point, Bethel, Kwigillingok, Mt. Village, and Kotzebue (Figure 2) (Nobmann et al. 1992). In that survey, fish was the most frequently eaten source of dietary protein; among all seafood items, salmon ranked highest in the species most often consumed (Nobmann et al. 1992). The mean of the daily intake of shellfish and fish for Alaska

Natives was 109 g (i.e., 3.82 ounces) compared with a 17 g average for participants in the National Health and Nutrition Examination Survey (NHANES) II: a greater than 6-fold higher fish intake among Alaska Natives than national consumption estimates.

In the eleven community survey, Alaska Native adults consumed more energy, protein, fat, carbohydrates, iron, vitamin A, and vitamin C, but less calcium, and fewer fruits and vegetables than did the general US adult population (NHANES II) (Nobmann et al. 1992). The survey also found that Alaska Native diets were supplemented by significant amounts of commercial and processed foods. Overall, the top 6 meat items most frequently mentioned in the dietary recall were salmon, beef, fish (other than salmon) and shellfish, pork (including bacon and ham), frankfurters (including sausages and luncheon meats), and chicken (Nobmann 1989). Similarly, in a Women Infants and Children (WIC) food recall survey for 46 children aged 1-5 in the Aleutian Islands, the most commonly mentioned food item was bologna (Smith et al. 1996).

In the eleven communities surveyed, liver and kidney consumption of wild harvested mammals or market meats was infrequently mentioned. However, as depicted in Figure 2, coastal villages with a heavy reliance upon marine mammals and interior villages with a greater reliance upon game meats were not represented in the survey. Thus, generalizations from the available survey data to all geographic areas of the state are not possible.

In a Behavioral Risk Factor Surveillance System survey, a similar percentage of Alaska Natives (20%) reported consuming 5

vegetable or fruit portions a day compared to non-Natives (18%), and residents in the lower 48 states (22%) (AKDHSS 1997). According to a recent focus group survey, barriers to fruit and vegetable consumption for Native and non-Natives include high cost, poor quality, and seasonal availability (Burnham 1996).

U.S. Dietary Intake Guidelines

The US Department of Agriculture recently issued dietary advice for Americans which includes the following:
- eat a variety of foods;
- balance the food you eat with physical activity;
- choose a diet with plenty of grain products, vegetables, and fruits;
- choose a diet low in fat, saturated fat, and cholesterol;
- choose a diet moderate in sugars;
- choose a diet moderate in salt and sodium;
- if you drink alcoholic beverages, do so in moderation.

In addition, the National Cancer Institute and the Produce for Better Health Foundation are jointly sponsoring a program to encourage eating 5 portions of fruits and vegetables a day. Vegetables and fruits are good sources of dietary fiber, vitamin C and A, and consumption of vegetables and fruits is being promoted to reduce the risk of chronic diseases such as cancer, heart disease and stroke in the general US population.[1]

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[1]For more information on nutrition and nutrition-related chronic diseases in Alaska, contact: Alaska Department of Health and Social Services, Division of Public Health, Section of Maternal, Child and Family Health, Nutrition Services Unit, 1231 Gambell Street, Anchorage, AK 99501, 269-3457.

References

AKDFG (1994). <u>Subsistence in Alaska</u>: Division of Subsistence, Alaska Department of Fish and Game: Update.

AKDHSS (1997). <u>Eat Smart Alaska! Nutrition-Related Chronic Disease in Alaska</u>: State of Alaska Department of Health and Social Services, Division of Public Health, Section of Maternal, Child and Family Health, Nutrition Services, Chronic Disease Nutrition Program: Needs Assessment.

Becker, P.R., E.A. Mackey, M.M. Schantz, R.R. Greenberg, B.J. Koster, S.A. Wise, D.C. G. Muir (1995). <u>Concentrations of Chlorinated Hydrocarbons, Heavy Metals and Other Elements in Tissues Banked by the Alaska Marine Mammal Tissue Archival Project</u>: U.S. DOC, National Institute of Standards and Technology: NISTIR 5620.

Burnham, S. (1996). <u>Focus Group Findings: Factors Associated With Fruit and Vegetable Consumption in Alaska</u>. Tenth International Congress on Circumpolar Health, Anchorage, AK, American Society for Circumpolar Health: 49.

Dewailly, E., J.J. Ryan, C. Laliberte, S. Bruneau, J.-P. Weber, S. Gingras, G. Carrier (1994). "Exposure of remote maritime populations to coplanar PCBs." <u>Environ Health Perspect</u> **102** (1):205-209.

Egede, I. (1996). <u>Oral Presentation</u>. Tenth International Congress on Circumpolar Health, Anchorage, Alaska, American Society for Circumpolar Health.

Heller, C.A., E.M. Scott (1967). <u>The Alaska Dietary Survey</u>: U.S. Govt. Printing Office: Public Health Serv. Publ. No. 999-AH-2.

Hovda, J. (1997). <u>Annotated Bibilography of Unpublished and Gray Literature on Persistent Organic Pollutants and Trace Metals in Alaska Marine Mammals From 1972 to 1997</u>: Environment and Natural Resources Institute, University of Alaska Anchorage.

Kuptana (1996). <u>Oral Presentation</u>. Tenth International Congress on Circumpolar Health, Anchorage, Alaska, American Society for Circumpolar Health.

Lentfer, J.W. (1988). <u>Selected Marine Mammals of Alaska. Species Accounts with Research and Management Recommendations</u>. Washington DC. Juneau AK, Marine Mammal Commission, GSA Printing 275.

Lowry, L.F.,F.H. Fay (1984). "Seal eating by walruses in the Bering and Chukchi Seas." <u>Polar Biol</u> **3**:11-18.

Muir, D., B. Grift, C. Ford, M. Segstro (1992b). "Spatial trends in organochlorines in arctic ringed seal and walrus." <u>Environmental Studies, Northern Contaminants Program</u> **68**:73-76.

Nobmann, E.D. (1989). <u>Dietary Intakes of Alaska Native Adults 1987-1988</u>: Alaska Area Native Health Service: Final.

Nobmann, E.D., T. Byers, A.P. Lanier, J.H. Hankin, M.Y. Jackson (1992). "The diet of Alaska Native adults: 1987-1988." <u>Am J Clin Nutr</u> **55**:1024-1032.

Pungowiyi (1996). <u>Oral Presentation</u>. Tenth International Congress on Circumpolar Health, Anchorage, Alaska, American Society for Circumpolar Health.

Smith, J., P. Easton, N. Rody (1996). <u>Use of Television for Alaska WIC Nutrition Education</u>: Alaska Department of Health and Social Services, Division of Public Health, Section of Maternal Child and Family Health.

Wei, C.K. (1973). "The Nutritional Status of Alaskan Eskimos with Respect to Fatty-Acids, Vitamin-A and Vitamin-E <u>Health Sciences, nutrition</u>. Urbana-Champaign, University of Illinois:111.

Benefits from Traditional Foods in Alaska

Background

The use of traditional foods provides a basis for cultural, spiritual, health, nutritional, medicinal, and economic well being among Alaska Natives and indigenous peoples. The social aspects of sharing in subsistence harvests and feasts associated with age-old traditions are integral to the cultural fabric of current-day Alaska Natives. Subsistence activities use local knowledge and skills and provide an opportunity to pass on knowledge from generation to generation, preserving cultural identity. Subsistence is also an opportunity for physical activity, self-reliance and meaningful productive work, especially in remote areas where wage paying jobs are few. Thus, traditional food (known as country food in Canada) is **"the basis of social activity and of the maintenance of social bonds through its production and distribution. This is the essence of subsistence not simply as an activity, but as a socio-economic system"** (Usher et al. 1995).

While the health relevance of chemical contaminants in subsistence foods is an area of uncertainty and scientific debate, with clinically relevant health risks usually too small to observe, the social and cultural disruption associated with food consumption advisories can have profound and measurable effects on the health and well-being of subsistence communities. For example, changes in diet, lifestyle, and the social and cultural disruption that follows the cessation of subsistence may contribute to a wide array of changes in communities from increases in obesity and diabetes, to increases in violence, alcoholism and drug abuse (Shkilnyk 1985; Wheatley 1994).

In addition to the socio-cultural and economic value of subsistence in Alaska, traditional foods provide known health benefits. In remote Alaska, grocery stores and supermarkets are rare and often poorly stocked. Small village stores sell convenience items including chips, canned soda and candy, have a limited supply of meat and dairy products, and usually lack fresh fruit and vegetables. Thus, there is often insufficient variety in products to provide healthy alternatives to traditional foods, and shopping excursions to major cities and shipping can be costly. The market foods that often replace locally harvested wildlife are high in saturated fat and vegetable oils and carbohydrates and often lower in nutrient value. In addition, dietary changes are complex in nature, often coinciding with a number of other lifestyle changes which also contribute to increases in chronic diseases such as heart disease, diabetes, and cancer.

Economic Benefits of Subsistence Foods

In addition to providing meaningful work and social interaction, traditional foods are of great economic value in Alaska. Traditional foods can be obtained with little or moderate costs compared to the cost of market foods, which are very expensive in Alaska particularly in remote areas inaccessible by road where food items must be imported by plane or boat. For example, food for a week for a family of four eating at home costs $200 in the village of Elim, (outside of Nome), $150 in Dillingham, and

$90 in Anchorage according to a 1994 survey (Alaska Cooperative Extension 1995). Statewide, the costs associated with replacing subsistence foods with market substitutes in rural Alaska is estimated to range from $131 to $218 million annually (AKDFG 1994). This dollar amount assumes a replacement expense of $3-5 a pound of wild harvest foods.

According to the Alaska Department of Fish and Game, the estimated per capita cash value of subsistence foods in the rural interior is valued at $3,063 per person compared with a per capita income of only $6,205, representing 49% of the average income of the area (AKDFG 1994). In other regions, the replacement costs for locally harvested food are estimated at 59% of the average Native family income in the western region, 31% in the arctic region, and 22% overall for rural Alaska (AKDFG 1994). Thus, replacing subsistence foods with market foods would present a considerable economic burden to Alaska Natives.

Nutritional Benefits of Traditional Foods - Overview

The traditional diet of wild game meats, fish, and in coastal areas, marine mammals, provides a diet rich in animal and fish protein, low in saturated fat, and rich in omega-3 polyunsaturated fatty acids. In addition, the plants, berries, and seaweeds in Alaska provide an important nutritional source of vitamins, minerals, and fiber. Vitamin C in traditional plants prevented scurvy in Alaska, and vitamin C is known to help fight infection, heal wounds, help prevent cancer, keep teeth and gums healthy, and help the body absorb iron. Vitamin A also helps fight infections, is good for night vision and for healthy bones,

teeth, and skin. Iron is needed to carry oxygen in the blood, fight disease, and provide energy and mental alertness to promote learning. Calcium is needed for strong bones, for normal blood clotting, and for a healthy nervous system.

Fats provide support for growth and development and the high energy needs of cold climates. However, excessive fat intake is a major cause of obesity, high blood pressure, certain types of cancer, and coronary heart disease. Cholesterol is also needed to help synthesize vitamin D and hormones and for the maintenance of cell walls. In excess, however, cholesterol is also associated with coronary heart disease risk.

Fats are divided into saturated and unsaturated fats, which refer to the number of hydrogen atoms in the fatty acid molecule's chemical structure. Saturated fats are found in dairy and domestic animal products, such as whole milk, cream, cheeses, beef and pork, and in tropical oils. Because dietary intake of saturated fats can increase serum cholesterol levels and heart disease risk, and has also been related to glucose intolerance and NIDDM, limiting one's intake of saturated fat is important. Unsaturated fats include monounsaturated and polyunsaturated fats. The two families of essential polyunsaturated fatty acids (PUFA) consist of the omega-6 and omega-3 PUFAs. The Western diet is typically high in saturated fat and in the omega-6 polyunsaturated fatty acids, particularly linoleic acid (18:2), and to a lesser extent arachidonic acid (20:4) derived from vegetable oils and meat sources. In contrast, the traditional diet, which is low in saturated fat and high in monounsaturated fat and omega-3 PUFAs from fish and marine oils, is considered to be more

healthy than the typical Western diet, especially beneficial in preventing heart disease and possibly beneficial in preventing non-insulin dependent diabetes mellitus (Feskens 1995; Storlien 1996).

In nutrient analyses of seven plants, conducted by the Mt. Edgecumbe Native Hospital and the Alaska Area Native Health Service, two dried seaweeds were found to be exceptional for their high nutrient content (Drury, 1985).

"One hundred grams (1 1/2 cups) of dried black or ribbon seaweed provides nearly one-half the adult Recommended Dietary Allowance (RDA) for protein, almost one-quarter the requirement for calcium, all the male requirement for iron and over half the iron needed by a female. One hundred grams of dried black seaweed contained 100% of the RDA for riboflavin, over half the allowance for niacin and vitamin A, and one-third the allowance for ascorbic acid" (Drury, 1985).

In another document, "What's In Alaskan Foods" (Jensen et al. 1994), prepared by the Nutrition Services of the Alaska Area Native Health Service, the nutritional composition of traditional foods was examined.

"Lowbush salmonberries, willow leaves, sourdock and lowbush cranberries are excellent sources of vitamin C (Figure 3). Only a half cup of lowbush salmonberries provides 100% of the daily nutritional requirement for vitamin C based upon a 2,000 calorie diet. Sourdock, wild rhubarb, fireweed, and salmonberries are excellent sources of Vitamin A (beta carotene) (Figure 4). Clams, seal flesh, cockles, ptarmigan,

moose, caribou, and venison are excellent sources of iron (Figure 5). Small fish can provide an important source of calcium in the diet, with as few as 3 sardines (with bones) providing nearly 40%, and 1 cup of kelp with herring eggs providing nearly 30% of the daily nutritional requirement for calcium." (Figure 6)

(Jensen et al. 1994)

Wild game meats (moose, caribou, and venison) are low in total fat compared to the meat products of domestic animal products. To illustrate, a three ounce serving of roasted moose, the leanest of game meats, provides 50% of the total daily requirement for protein (based upon a 2,000 calorie diet), with only 1% of the suggested maximum recommended intake of total fat and 5.7 % of the total daily caloric intake (assuming a diet of 2,000 calories a day) (Figure 7) (Jensen et al. 1994). In contrast, a 3 ounce serving of beef and pork frankfurters provides only 19% of the total daily requirement for protein, with 38% of the suggested maximum recommended intake of total fat and 13.6% of the total daily calorie intake (Figure 7) (USDA 1997). In addition, moose, caribou and venison are greater sources of iron than are beef and pork frankfurters.

Comparison of the saturated and unsaturated fats in traditional and market foods illustrates the high unsaturated fat content of seal oil and hooligan grease compared to lean hamburger, butter, and American cheese (Figure 8) (Jensen et al. 1994). Also, while the percent of the total unsaturated fat content of seal oil is comparable to that of corn oil and peanut butter, the unsaturated fats in these food items are substantially different in the proportion of monounsaturated fatty acids

and in the type of polyunsaturated fatty acids they contain. Peanut butter contains a high proportion of monounsaturated fatty acids as does seal oil and olive oil, while corn oil contains a high proportion of polyunsaturated fat in the form of the omega-6 PUFA, linoleic acid (18:2). Marine mammal oils and fish oils vary in the proportion of monounsaturated fatty acids and of omega-3 PUFAs present and in the chemical structure of the varying forms of monounsaturates and polyunsaturates. Researchers at Louisiana State University found that the omega-3 PUFA content of some marine mammals and fish ranged from 15-45% of total fatty acids present (Malcom et al. 1996). Fish and marine mammals, and to a lesser extent shellfish, are the only significant direct dietary source of omega-3 PUFAs: eicosapentaenoic acid (EPA, 20:5) and docosahexaenoic acid (DHA, 22:6).

In addition to providing omega-3 PUFAs to the diet, marine mammals and fish are also excellent sources of protein and contain other nutrients in varying quantities depending upon species. A 3-ounce serving of ringed seal provides 48% of the daily requirement for protein, 4% of the daily requirement for total fat, 92% of the daily requirement for iron, and 18% of the daily requirement for vitamin A (Figure 9) (Jensen et al. 1994). A 3-ounce serving of cooked King Salmon provides 40% of the daily requirement of protein, 9% of the daily requirement for iron, and 7% of the daily requirement for vitamin A (Jensen et al. 1994).

Benefits of Omega-3 Fatty Acids

Great interest exists in studying the beneficial effects of dietary seafood that is high in omega-3 fatty acids. This interest traces its origins to two Danish physicians,

Bang and Dyerberg, who in 1970 observed a low incidence of cardiovascular diseases in Greenland Eskimos and who showed a strong association between this lack of heart disease and a marine-based diet (Bang et al. 1972; Bang et al. 1976; Dyerberg et al. 1978). Many subsequent studies have documented many important beneficial effects of omega-3 fatty acids (Bang et al. 1980; Dyerberg 1989).

Omega-3 fatty acids are polyunsaturated fatty acids in which the first double bond occurs between the third and fourth carbon atoms from the methyl terminal of the fatty acids. The most abundant long chain omega-3 fatty acids are EPA (eicosapentanoic acid, 20:5) and DHA (docosahexanoic Acid, 22:6). These are found in phytoplankton, consumed in the food chain, and found in seafood in high amounts (Malasanos et al. 1991).

Saturated fatty acids have no carbon to carbon double bonds and are found mostly in animal tissue (e.g., stearic, palmitic). Linoleic acid is an omega-6 fatty acid -- the first double bond from the methyl terminal of the fatty acid is between the sixth and seventh carbon atoms. Linoleic acid is present in many vegetable oils (Malasanos et al. 1991).

Omega-3 fatty acids cannot be synthesized by humans. Omega-3 fatty acids exist in high amounts in marine mammals and fish. Marine mammals also have high amounts of monoene lipids. Two highly active families of compounds are derived solely from omega-3 and omega-6 fatty acids, prostaglandins and leukotrienes. Derived from omega-3 fatty acids are those prostaglandins that are anti-thrombogenic while those from omega-6 fatty acids are highly thrombogenic. Prostaglandins

(thromboxanes and prostacyclines) are highly vasoactive and very important in clotting of blood (Malasanos et al. 1991). Leukotrienes are very important in inflammation and the immune system. Omega-3 fatty acids inhibit chemotaxis and migration of monocytes and attentuate the inflammatory response.

The role of diet in disease patterns is complex. There are many aspects of dietary change that may influence nutritional status and disease occurrence too numerous to review here. Thus, we limited the following review of the literature to the role of omega-3 PUFAs and the balance of omega-6 to omega-3 PUFAs in a healthy diet.

A dietary shift from fish, marine mammals, wild game meats and plants to a typical western diet rich in saturated fat from dairy and meat products and linoleic acid from vegetable oils changes the balance between omega-6 and omega-3 fatty acids. Most humans (with the exception of preterm infants and possibly individuals with certain genetic disorders), can produce DHA from precursor fatty acids: EPA and alpha-linolenic acid (ALA). Excess amounts of the omega-6 PUFAs in the diet are believed to inhibit the production of DHA and EPA from the precursor fatty acid, ALA which is found in dark green vegetables and certain nuts and seed oils.

Thus, significant dietary increases in omega-6 vegetable oils and decreases in the dietary intake of DHA and EPA (oils from fish and marine mammals) results in an increased ratio of omega-6: omega-3 PUFAs in the diet. It is estimated that diets relying upon fish, wild game and plants provide a 1:1 omega-6 to omega-3 ratio and that in the current Western diet that the ratio may be as

high as 8:1 or 10:1 (Eaton et al. 1985). The dietary imbalance between omega-6: omega-3 leads to a high proportion of arachidonic acid (AA) and diminished EPA and DHA in cell membranes of tissues. EPA and AA are precursors for the biologically active metabolites, eicosanoids, which modulate many cell functions. The nature and degree of biological activity of the eicosanoids are dependent upon whether they are derived from the omega-3 or omega-6 PUFAs.

The scientific literature explores the potential influence of omega-3 deficiency or supplementation on a variety of chronic diseases, including arthritis and inflammation, depression, skin disorders, diabetes, cardiovascular disease, eye disorders, cancer and cancer therapy, neonatal growth and development, pregnancy outcome, and immune function (NIH 1995). Many of these areas of research are too new and exploratory for definitive statements about the potential impact of dietary changes in the omega-6: omega-3 ratio. Also, it should be noted that considerable debate exists regarding the optimal ratio of omega-6 to omega-3 PUFAs in the diet. For example, high intake of omega-3 PUFAs can suppress the immune system, which can have both beneficial effects (particularly in protecting against or ameliorating autoimmune disease) and potentially negative consequences in fighting infections (NIH 1995). Also, while reduced platelet aggregation and blood clotting would provide cardiovascular benefits, prolonged bleeding time associated with the high consumption of omega-3 PUFAs could represent an acute health hazard during traumatic injuries.

We limit the following review of the literature to the role of omega-3 PUFA's in

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three research areas: neonatal growth and development and healthy pregnancies, cardiovascular disease, and diabetes.

Neonatal Growth and Development and Healthy Pregnancies

Polyunsaturated fatty acids, predominately in the form of DHA are present in large amounts in the grey matter of the brain, nerve synapses, the retina of the eye and other specific body locations (OBrien et al. 1964; Anderson 1970; Tinoco et al. 1977). During the third trimester, omega-3 fatty acids are selectively mobilized to meet the demands of increased neural and vascular growth (Clandinin et al. 1980; Martinez et al. 1988). In fact, 70% of all adult brain cells are formed before birth. Omega-3 fatty acids and the ratio of omega-6 to omega-3 fatty acids are important for optimal brain and retinal development, maturation of the visual cortex, and motor skill development; they may also enhance the duration of quiet sleep episodes in human infants (Carlson et al. 1993; Innis et al. 1994; Uauy-Dagach et al. 1995; Uauy et al. 1996). Premature babies breastfed or fed infant formula containing DHA and AA have superior eye and neurobehavioral development than those fed infant formula not supplemented with DHA and AA (Lanting et al. 1994).

The longer gestational age and heavier birthweights of the Faroe Island population (Olsen et al. 1985) led researchers to speculate that marine oils from fish and whales could potentially increase gestational age and birthweight and thereby enhance the survival and health of newborns (Olsen et al. 1986). A fish oil supplementation study during the third trimester of pregnancy was conducted in Denmark and found that fish oil supplementation was related to increased

gestational age and birth weight (Olsen et al. 1990). In another study, a small but significant variation in birthweight was associated with residence in the Orkneys where fish consumption is 30% higher than the Aberdeen comparison group examined (Harper et al. 1991).

In a fish oil supplementation trial among women at risk for preterm delivery, fish oil supplementation reduced the prevalence of preterm deliveries and was associated with non-statistically significant reductions in pregnancy-induced hypertension (Olsen et al. 1992).

Findings of diminished omega-3 PUFAs in cell membranes during lactation and pregnancy (Holman et al. 1991) have led some nutritionists to speculate a need for omega-3 PUFA supplementation during pregnancy to ensure that an adequate supply of essential fatty acids is available to promote optimal brain and visual development (Uauy-Dagach et al. 1995). Oily fish or marine mammal consumption will increase a woman's fat stores of DHA and will ensure an adequate supply of DHA to promote optimal brain development.

Reduction in Cardiovascular Disease

Initial observations of a decreased prevalence of ischaemic heart disease among the Greenland Eskimos prompted investigations into the possible beneficial effects of fish and marine oils. Greenlandic Eskimos have significantly lower levels of total cholesterol and triglycerides and higher levels of high-density-lipoproteins, and decreased platelet aggregability than Danish comparisons (Bang et al. 1971; Dyerberg et al. 1979).

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To date, fish consumption has been related to a reduced risk of coronary heart disease in two case-control studies, six prospective studies, and an intervention trial (Kromhout et al. 1985; Shekelle et al. 1985; Norell et al. 1986; Burr et al. 1989; Gramenzi et al. 1990; Shekelle et al. 1993; Siscovick et al. 1995; Albert et al. 1996; Daviglus et al. 1997). The protective effect is reflected to a large degree upon a reduction in myocardial infarction deaths. In the Chicago Western Electric Study, for example, men who consumed 35 g or more of fish per day had a 42 percent lower rate of death from myocardial infarction than non fish consumers (Daviglus et al. 1997).

While not all studies show a protective effect of fish consumption on coronary heart disease (Curb et al. 1985; Vollset et al. 1985; Ascherio et al. 1995; Morris et al. 1995), fish and fish oils are known to have a favorable effect on a variety of factors that are known or suspected of reducing cardiovascular disease risk (Schmidt et al. 1994). A high intake of omega-6 to omega-3 PUFAs in the diet results in an overproduction of eicosanoids derived from omega-6 PUFAs. (Eicosanoids derived from arachidonic acid (AA) include thromboxane (TX) A_2, prostacyclin (PGI_2) and leukotriene (LT)B_4. Whereas eicosanoids derived from EPA include TXA_3, PGI_3, and LTB_5 (Schmidt et al. 1994). The overproduction of eicosanoids derived from omega-6 PUFAs is considered a mechanism in which heart disease risk would be elevated through eicosanoids effects on vasoconstriction, clotting, platelet-vessel wall interaction, and other parameters. Dietary intake of omega-3 shifts the eicosanoid balance from proaggregatory and vasoconstrictory to antiaggregatory and vasodilatory (Dyerberg et al. 1978; Schmidt et al. 1994).

Additional anti-atherosclerotic effects of omega-3 includes the suppression of smooth muscle cell proliferation, reduced adhesion of leukocytes to endothelial cells, reduced chemotaxis of neutrophils and monocytes, reduced very low density lipoprotein cholesterol and triglyceride levels, and increased erythrocyte distensibility (Schmidt et al. 1994). In addition, there is some evidence that omega-3 PUFAs lower systolic and diastolic blood pressure (Appel et al. 1993). However, studies are limited, sample sizes are small (median of 31 individuals with a range of 11 to 350), and the duration of follow-up generally of short-term (Appel et al. 1993).

A study of cardiovascular deaths during 1980-1986 in Alaska found that the average annual, age-adjusted death rate from cardiovascular diseases and atherosclerosis among Alaska Natives was lower than among Alaska non-Natives (162.0 vs. 242.1; RR=0.67) while death rates from other causes were higher (954.4 vs. 618.6; RR=1.54). These findings suggested that Alaska Natives had less atherosclerosis than other populations (Middaugh 1990).

Further research to explore this possibility was conducted in an autopsy study in Alaska to evaluate the extent of atherosclerotic lesions in the coronary arteries and aortas from Alaska Natives and non-Natives. Standardized comparisons between Alaska Natives and non-Natives showed that the extent of atherosclerotic lesions increased with age in both groups, but the prevalence of raised lesions in Natives was significantly lower than in non-Natives (Boudreau et al. 1993; Newman et al. 1993).

In a subsequent autopsy study conducted in Greenland and Alaska, adipose fatty acid composition and lesion data were examined

(Newman et al. 1996). Among 129 Alaska Natives, 101 Greenland Natives, and 115 Alaska non-Natives, greater concentrations of adipose long chain omega-3 PUFAs (20:5, 22:5, and 22:6) were significantly associated with decreases in surface involvement with atherosclerotic lesions in the coronary arteries. These studies suggest that the differences in cardiovascular heart disease mortality between Alaska Natives and non-Natives are, at least in part, due to less atherosclerosis in Alaska and Greenland Natives (Newman et al. 1993; Newman et al. 1996).

Each year, approximately 670 Alaskans die of cardiovascular disease. The major components of CVD, heart disease and stroke, account for 26.7% of all Alaska deaths.

CVD is not just a disease of the elderly. Coronary heart disease kills a substantial number of relatively young people, especially men, in their most productive years of life. In Alaska, 35% of all coronary heart disease deaths occur among people under age 65 years.

In 1950 the major cause of death among Alaska Native people was infectious diseases, and the mortality rate from CVD was much higher among non-Native people than among Native people. By the 1980's, cancer, heart disease and injuries had become the leading causes of death among Alaska Natives as well as among non-Natives. Furthermore, the CVD rate fell dramatically among non-native people so that Alaska Natives now have higher CVD mortality rates than do non-Natives.

Alaska's mortality rate from heart disease in 1994 was lower than that for the U.S. (120.5/100,000 (Alaska) vs. 140.0/100,000 (U.S.) age-adjusted to U.S. 1940 population). The changing patterns of disease in Alaska reflect the increased overall life-expectancy of the population and increases in smoking, decreases in physical activity, changes in dietary practices, and increased obesity (Middaugh 1997; Middaugh 1997).

Prevention of Diabetes and its Complications

Ever since the initial reports of the rarity of diabetes in Alaskan and Greenland Eskimos (Scott et al. 1957; Sagild et al. 1966; Mouratoff et al. 1967; Kromann et al. 1980), omega-3 fatty acids have been thought to have a potential beneficial role in diabetes prevention and in preventing or delaying complications of diabetes (Lardinois 1987; Storlien et al. 1991; Raheja et al. 1993; Adler et al. 1994). Most research to date, however, has focused on the potential role of fish oils on lipids and glycemic control in persons with diabetes. Fish oils appeared to have a beneficial effect on glycemic control in patients with insulin dependent diabetes mellitus in several studies (Bagdade et al. 1990; Landgraf-Leurs et al. 1990). In addition, fish oils decrease serum triglycerides, and most studies show no effect on low-density lipoprotein (LDL) cholesterol (Puhakainen, 1995). Thus, these studies suggest that fish oils may be beneficial.

However, results of studies of the effect of fish oils on glycemic control in NIDDM patients are conflicting (Glauber et al. 1988; Friday et al. 1989; Hendra et al. 1990; Annuzzi et al. 1991; Fasching et al. 1991; Axelrod et al. 1994; Puhakainen et al. 1995; McManus et al. 1996). While most studies suggest that fish oil supplementation may

have an adverse impact on glycemic control, direct comparison of study findings are difficult because of differences in study design considerations. The clinical fish oil supplementation trials conducted to date examined small numbers of individuals, used different inclusion criteria, different numbers of weeks or months of follow-up and dosages, and several studies did not control for changes in caloric intake (Puhakainen, 1995). These study design differences greatly hinder the direct comparison of results and may explain the discrepancies in study findings.

In animal laboratory studies, rats fed diets high in omega-6 fatty acids (safflower oil) developed insulin resistance, whereas fish oil restored normal insulin action (Storlien et al. 1991). These and other laboratory data suggest that a deficiency in EPA and DHA or a high omega-6 to omega-3 fat ratio (which would prevent desaturase enzymes from forming EPA and DHA from ALA) may contribute to insulin resistance (Storlien et al. 1991). In addition, saturated fat intake is clearly related to the develoment of insulin resistance in both laboratory and epidemiological studies.

In an epidemiologic study of Yup'ik Eskimo and Athabaskans living in 15 villages near the Yukon and Kuskokwim Rivers, daily consumption of seal oil or salmon was associated with a lower risk of non-insulin dependent diabetes mellitus and impaired glucose tolerance (Adler et al. 1994). The protective effect was observed after controlling for age, ethnicity, body mass index, and gender. In that study eating seal oil fewer than 5 times per week did not confer protection.

The prevalence of diabetes, which was once rare among Alaskan and Canadian Eskimos,

has been steadily increasing (Scott et al. 1957; Mouratoff et al. 1967; Mouratoff et al. 1973; Schraer et al. 1988). In a survey of medical records from 1979-1985, the overall age-adjusted prevalence of diabetes mellitus (Type I and Type II) was 27.2 per 1,000 among the Aleuts, 22.0 among Alaskan Indians, and 8.8 per 1,000 among Alaskan Eskimos, compared to an overall U.S. rate of 24.7 per 1,000. In addition, gestational diabetes represents an emerging public health problem: the prevalence of diabetes during pregnancy among Yup'ik Eskimos is nearly twice that of the general U.S. population (Murphy et al. 1993).

Increases in saturated fat, caloric and carbohydrate intake, obesity and changes in physical activity and the proportion of nutrients in the diet are potential contributing factors to increasing NIDDM. For example, it is reported that there was no diabetes in the Akwesasne of Canada 50 years ago and that the prevalence of diabetes on the reserve is now four times greater than the Canadian average. The population at Akwesasne have changed their eating habits from a high fish protein diet to a high carbohydrate diet following information regarding PCBs in the St. Lawrence River (Wheatley 1994). Also, other changes are likely to have coincided with the noted dietary shift away from fish protein and an increase in carbohydrate intake, such as increases in saturated fat and total caloric intake, and increases in obesity and reduction in physical activity. A combination of inter-related factors likely contributed to the observed increase in NIDDM among the Akwesasne.

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Recommendations

Harvest and consumption of wildlife in Alaska provide important cultural, economic, nutritional and health benefits. Scientific evidence documents the nutritional superiority of many traditional foods. Future work to characterize the nutrient value and health benefits of traditional foods is greatly needed so that this information can be incorporated into each individual's decision-making about their personal dietary choices. Dietary surveys throughout Alaska will help identify nutritional deficiencies and can be used to promote educational campaigns to ensure healthy eating habits. Educational programs targeting youth regarding the value of traditional foods and the role of diet in promoting health are also needed.

Poorly researched or misleading general media coverage regarding the presence of contaminants in traditional foods can be very destructive to health and well-being. Inaccurate information erodes confidence in traditional foods and may result in unforeseen consequences in a population, increasing the consumption of market foods high in carbohydrates, sugars, and saturated fats that are often inferior in nutrient value. These dietary changes will increase the incidence of diabetes, cardiovascular disease, dental carries, and certain cancers.

The magnitude of risk associated with drastic shifts in diet and lifestyle in a population are high and measurable compared to the nature and much lower risk associated with cadmium, methylmercury, and polyhalogenated diaromatic hydrocarbons in Alaska traditional foods. The Alaska Division of Public Health fully supports the consumption of traditional foods.

Figure 1:   Composition of Subsistence Harvest By Rural Alaska Residents, 1990s
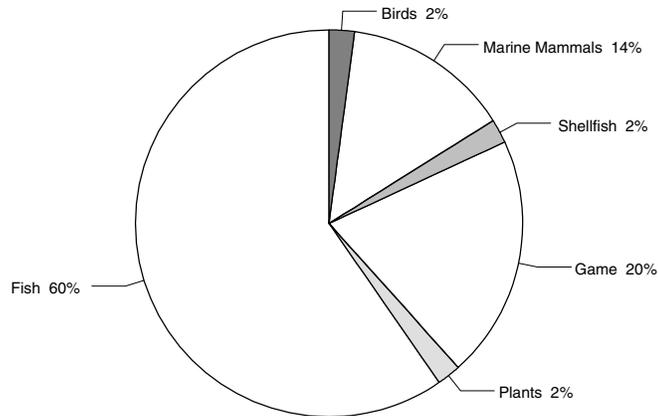
Source: (Alaska Department of Fish and Game 1994)

Figure 2:   Locations of the Eleven Communities Participating in the Alaska Area Native Health Service Study of Dietary Intake of Alaska Native Adults, 1987-1988

Mark Rhodes
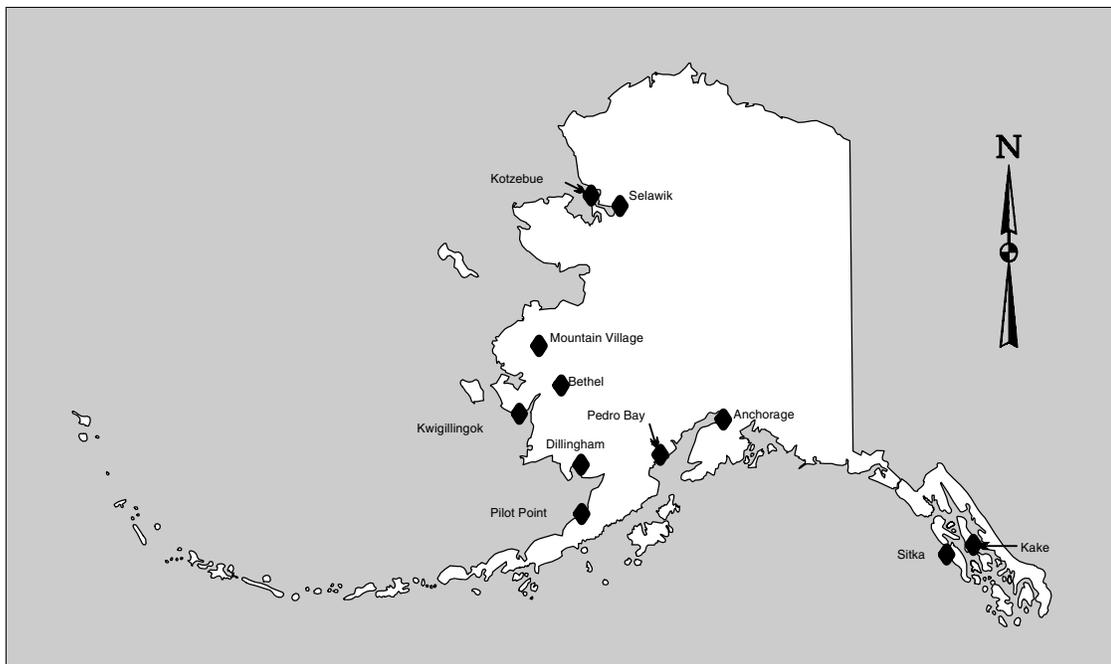
Source: (Nobmann 1989)

Figure 3:   Vitamin C in Selected Foods (Percent Daily Value in 1/2 Cup)
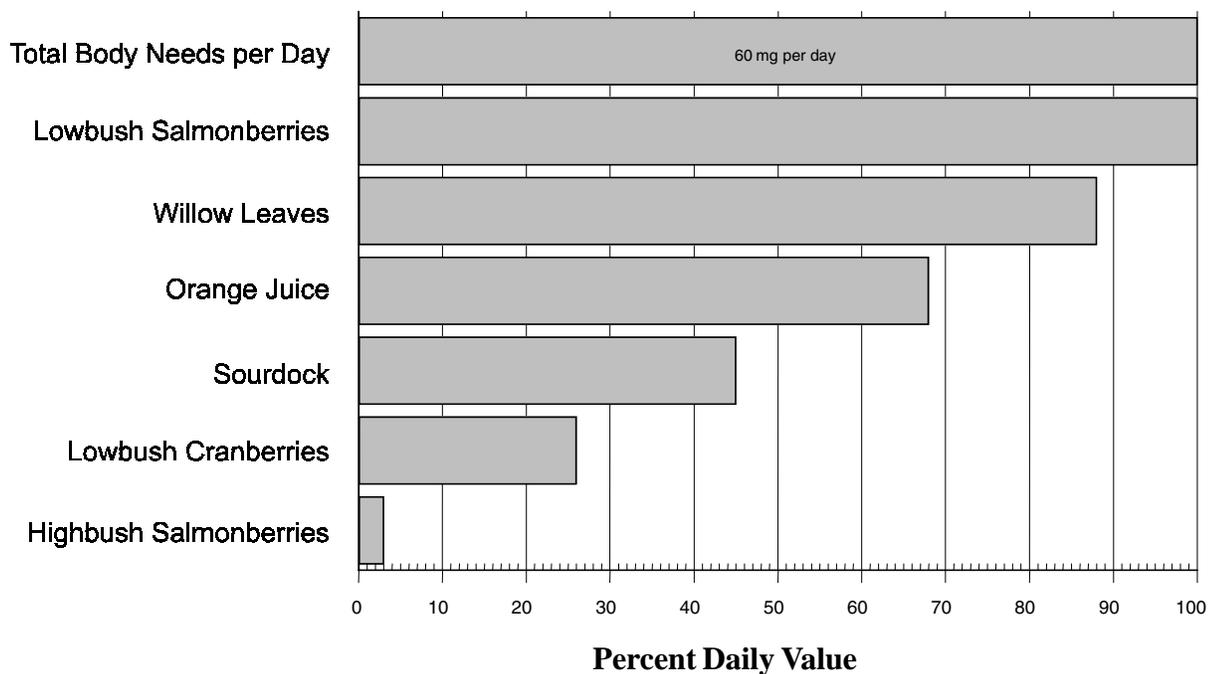
Source: Alaska Area Native Health Service, Nutrition Services (Jensen and Nobmann 1994).

Figure 4:   Vitamin A in Selected Raw Foods (Percent Daily Value in 1/2 Cup)
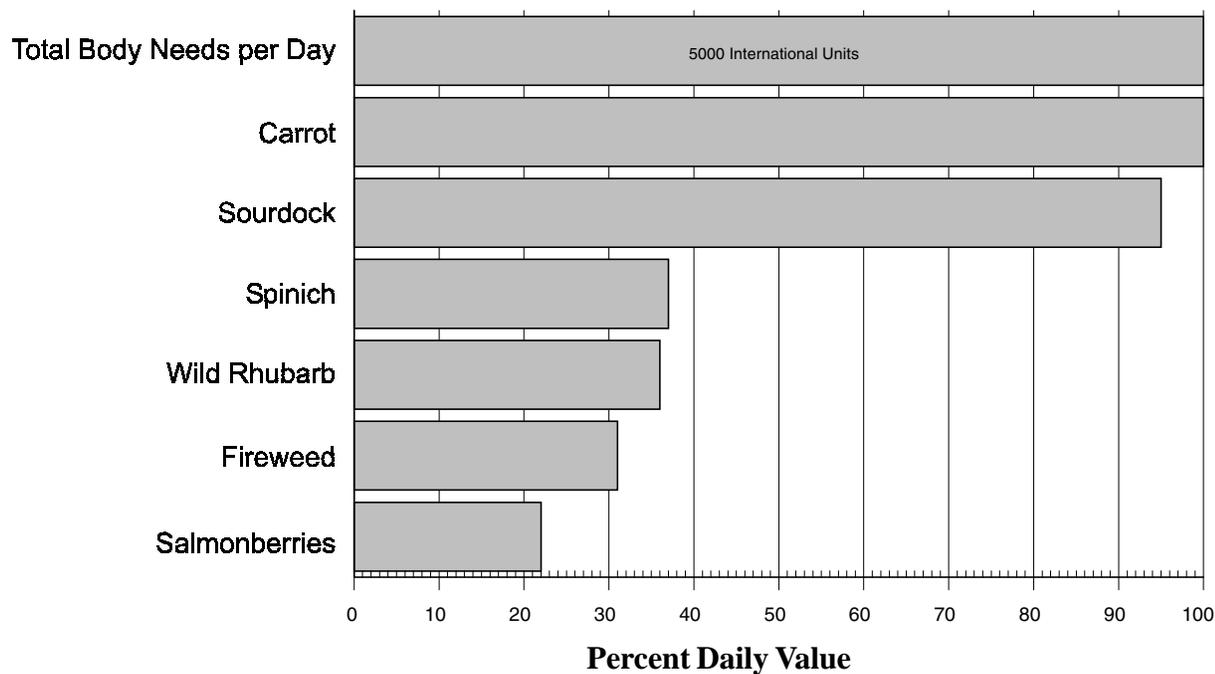
Source: Alaska Area Native Health Service, Nutrition Services (Jensen and Nobmann 1994).

Figure 5:   Iron in Selected Foods (Percent Daily Value in a Serving)
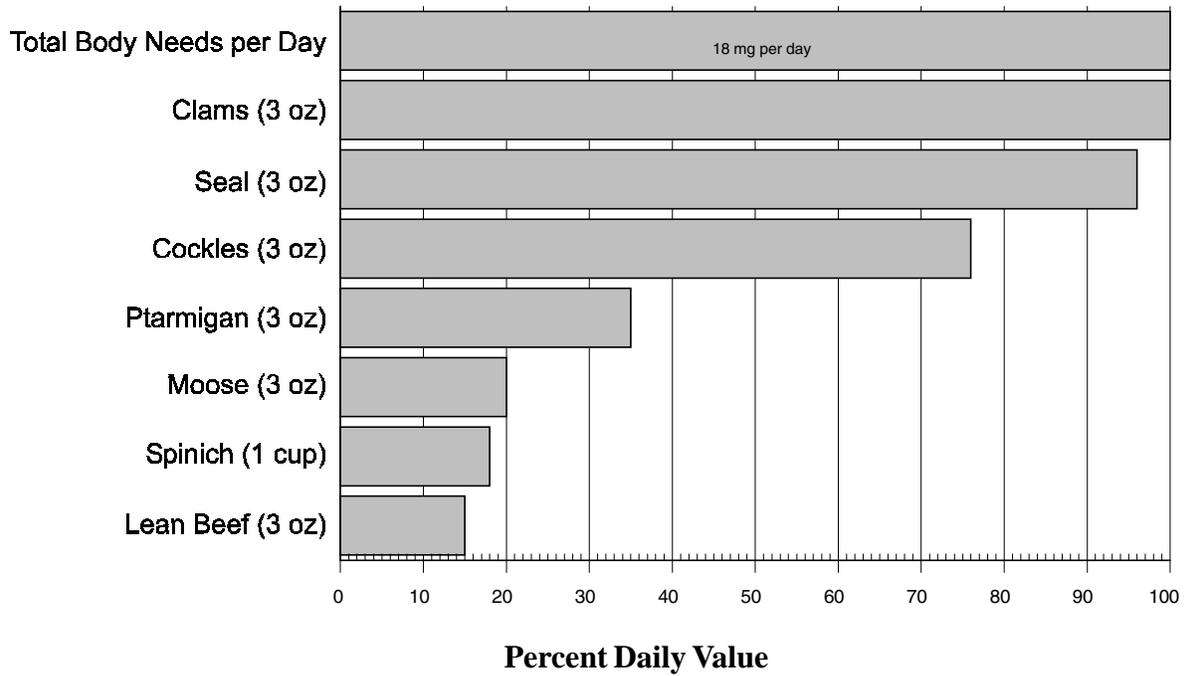
Source: Alaska Area Native Health Service, Nutrition Services (Jensen and Nobmann 1994).

Figure 6:   Calcium in Selected Foods (Percent Daily Value in a Serving)
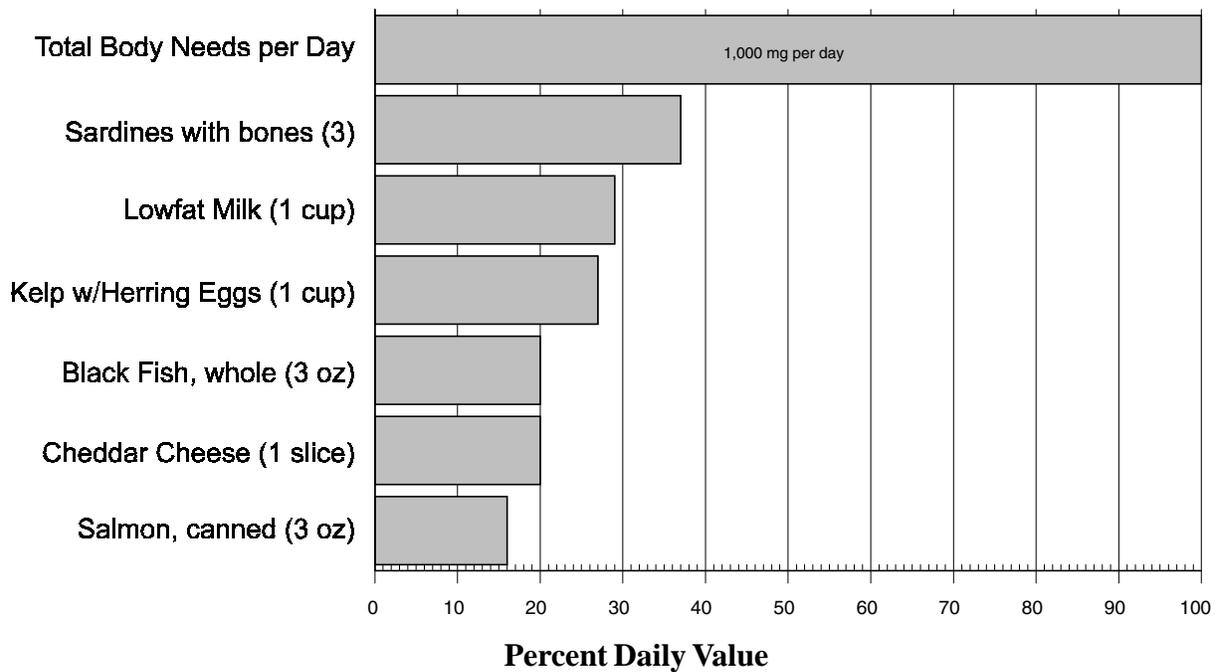
Source: Alaska Area Native Health Service, Nutrition Services (Jensen and Nobmann 1994).

Figure 7: **Percent Daily Value of Nutrients in Moose (Roasted) and Beef and Pork Frankfurters (3 Ounces).**

Percent Daily Value
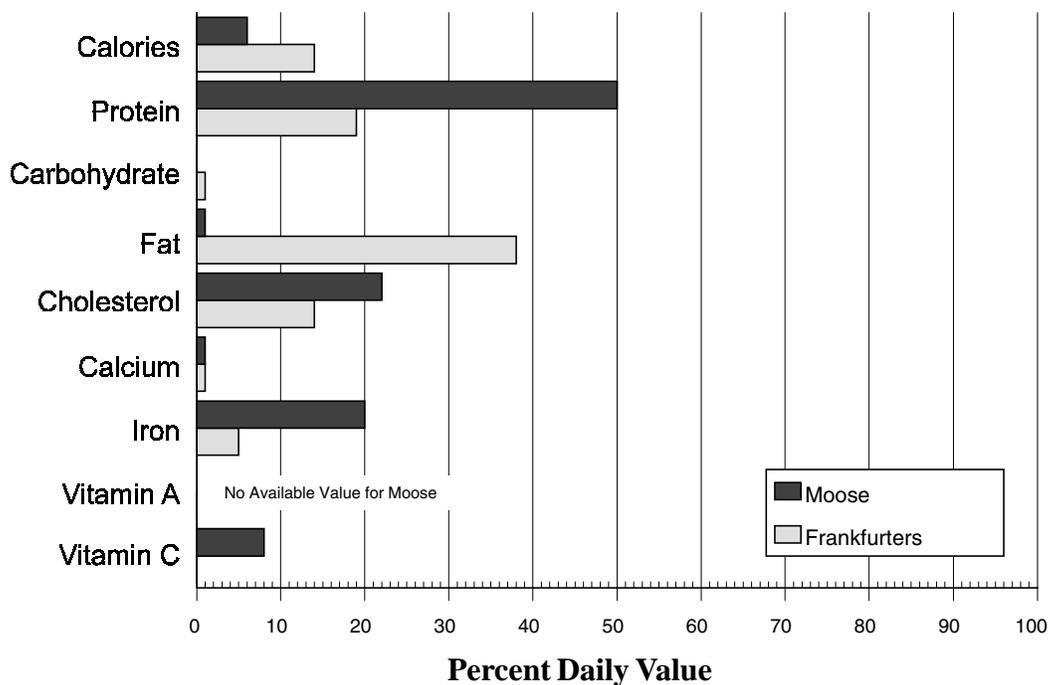
Source: Alaska Area Native Health Service, Nutrition Services (Jensen and Nobmann 1994, and USDA, 1996).

Figure 8: **Percent Saturated and Unsaturated Fat in Selected Foods in 1/4 Cup**
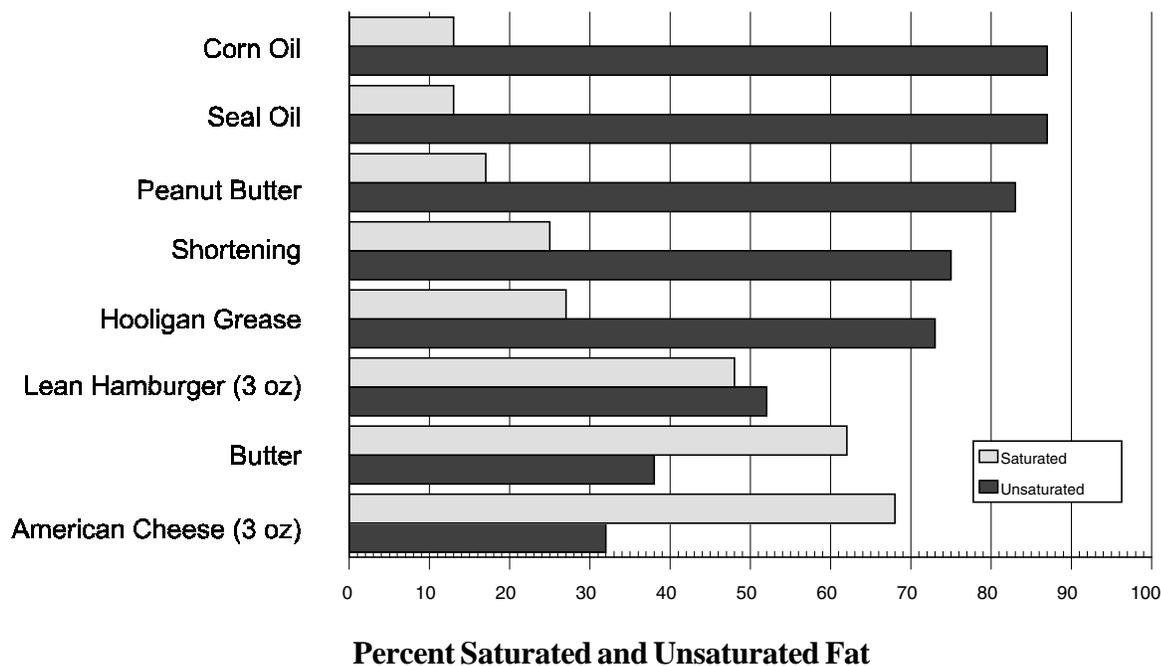
Percent Saturated and Unsaturated Fat

Source: Alaska Area Native Health Service, Nutrition Services (Jensen and Nobmann 1994).

Figure 9:   Percent Daily Value of Nutrients in Ringed Seal Flesh (3 ounces)
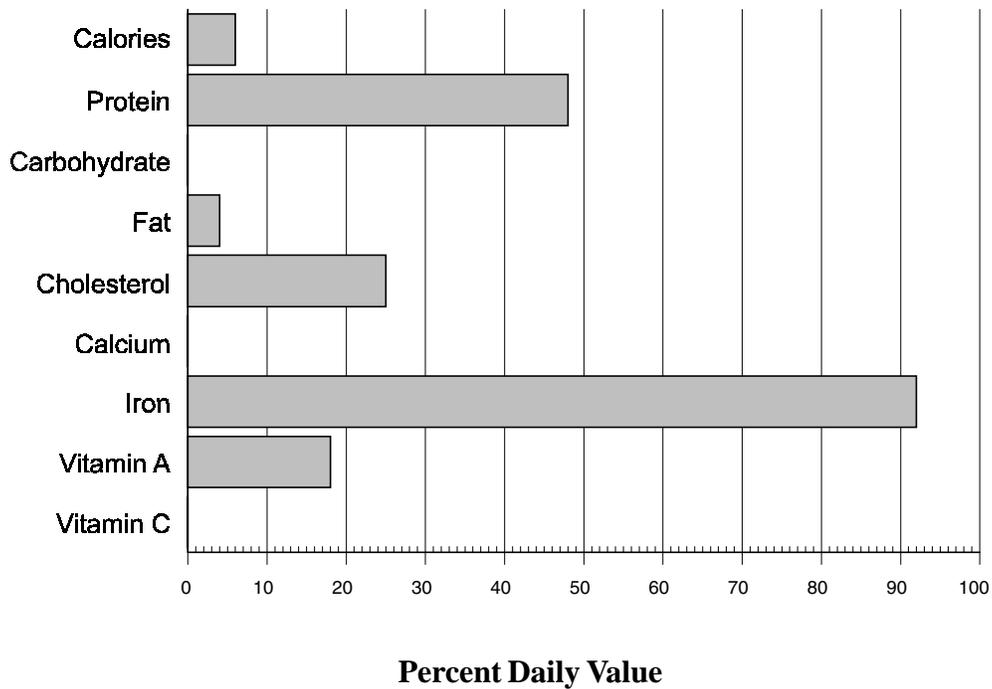
Percent Daily Value

Source: Alaska Area Native Health Service, Nutrition Services (Jensen and Nobmann 1994).

Figure 10:   Percent Daily Value of Nutrients in King Salmon (3 ounces)

Percent Daily Value
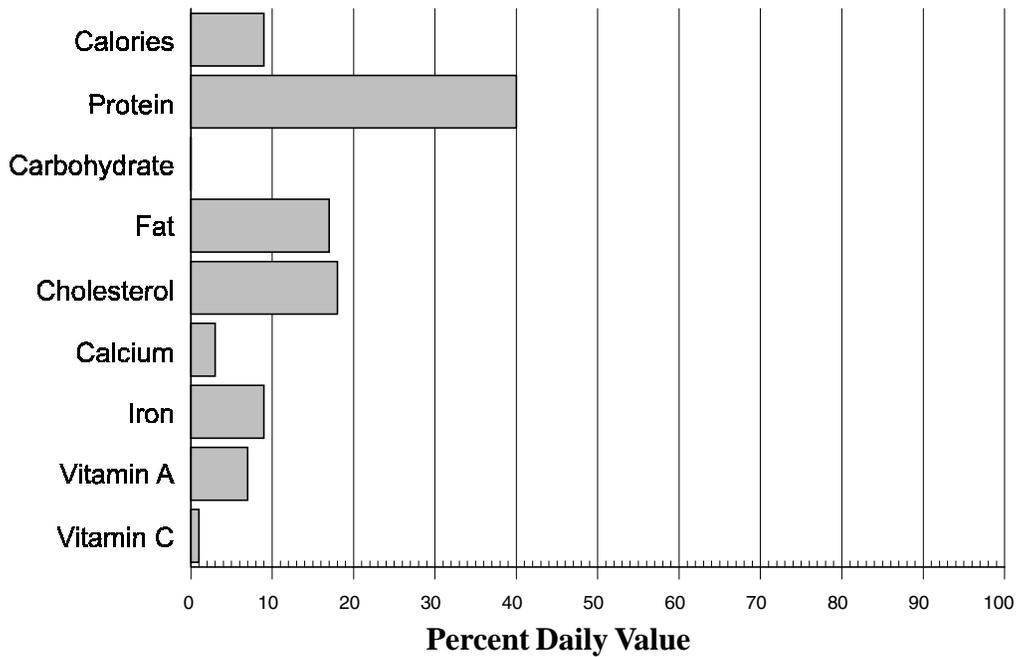
Source: Alaska Area Native Health Service, Nutrition Services (Jensen and Nobmann 1994).

References

Adler, A.I., E.J. Boyko, C.D. Schraer, N.J. Murphy (1994). "Daily consumption of seal oil or salmon associated with lower risk of non-insulin dependent diabetes mellitus and impaired glucose tolerance in Yup'ik Eskimo and Athabaskan Indians of Alaska." Arct Med Res **53**(2):271-275.

AKDFG (1994). Subsistence in Alaska: Division of Subsistence, Alaska Department of Fish and Game: Update.

Alaska Cooperative Extension (1995). Cost of Food at Home for a Week in Alaska: University of Alaska.

Albert, C.M., J.E. Manson, C.J. O'Donnell, U.A. Ajani, C.H. Hennekens (1996). Abstract: Fish Consumption and Risk of Sudden Death in the Physicians' Health Study from 69th Scientific Sessions, New Orleans. American Heart Assoc. Nov. 10-13, 1996. Circulation 94 I-578 (1996).

Anderson, R.E. (1970). "Lipids of ocular tissues. IV. A comparison of the phospholipids from the retina of six mammalian species." Exp Eye Res **10**:339-344.

Annuzzi, G., A. Rivellese, B. Capaldo (1991). "A controlled study on the effects of n-3 fatty acids on lipid and glucose metabolism in non-insulin-dependent diabetic patients." Atherosclerosis **87**:65-73.

Appel, L.J., E.R. Miller, A.J. Steidler, P.K. Whelton (1993). "Does supplementation of diet with 'fish oil' reduce blood pressure? A meta-analysis of controlled clinical trials." Arch Intern Med **153** (Jun 28):1429-1438.

Ascherio, A., E.B. Rimm, M.J. Stampfer, E.L. Giovannucci, W.C. Willett (1995). "Dietary intake of marine n-3 fatty acids, fish intake, and the risk of coronary disease among men." N Engl J Med **332** (15):977-82.

Axelrod, L., J. Camuso, E. Williams, K. Kleinman, E. Briones, D. Schoenfield (1994). "Effects of a small quantity of omega-3 fatty acids on cardiovascular risk factors in NIDDM." Diabetes Care **17**(1):37-44.

Bagdade, J.D., W.E. Buchanan, R.A. Levy, P.V. Subbaiah, M.C. Ritter (1990). "Effects of omega-3 fish oils on plasma lipids, lipoprotein composition, and postheparin lipoprotein lipase in women with IDDM." Diabetes **39**(4):426-431.

Bang, H.O., J. Dyerberg (1972). "Plasma lipids and lipoproteins in Greenlandic west coast Eskimos." Acta Med Scand **192**:185.

Bang, H.O., J. Dyerberg (1980). "Lipid metabolism and ischiemic heart disease in Greenland Eskimos." Adv Nutr Res **3**:1-22.

Bang, H.O., J. Dyerberg, N. Hjorne (1976). "The composition of food consumed by Greenland Eskimos." Acta Med Scand **200**:69-73.

Bang, H.O., J.Dyerberg, A.B. Nelson (1971). "Plasma lipid and lipoprotein pattern in Greenlandic West coast Eskimos." Lancet **1**:1143-1146.

Boudreau, D.A., J.P. Middaugh, J. Misfeldt, H.S. Pedersen, W.P.I. Newman, G.T. Malcom (1993). "Meeting report of Arctic Native atherosclerosis and omega 3 fatty acids." Arct Med Res **52**:73-75.

Burr, M.L., J.F. Gilbert, R.M. Holliday, P.C. Elwood, A.M. Fehily, S. Rogers, P.M. Sweetnam, N.M. Deadman (1989). "Effects of changes in fat, fish, and fibre intakes on death and myocardial reinfarction: diet and reinfarction trial (DART)." Lancet Sep **30**:757-761.

Carlson, S.E., S.H. Werkman, P.G. Rhodes, E.A. Tolley (1993). "Visual-acuity development in health preterm infants: effect of marine-oil supplementation." Am J Clin Nutr **58**:35-42.

Clandinin, M.T., J.E. Chappell, S. Leong, T. Heim, P.R. Swyer, G.W. Chance (1980). "Intrauterine fatty acid acretion rates in human brain; implications for fatty acid requirements." Early Hum Dev **4**:121-129.

Curb, J.D., D.M. Reed (1985). "Fish consumption and mortality from coronary heart disease." N Engl J Med **318**:821-822.

Daviglus, M.L., J. Stamler, A.J. Orencia, A.R. Dyer, K. Liu, P. Greenland, M.K. Walsh, D. Morris, R.B. Shekelle (1997). "Fish consumption and the 30-year risk of fatal myocardial infarction." N Engl J Med **336**:1046-1053.

Drury, H.M. (1985). "Nutrients in Native foods of Southeastern Alaska." J. Ethnobiology 5:87-100.

Dyerberg, J. (1989). "Coronary heart disease in Greenland Inuit: a paradox. Implications for western diet patterns." Arct Med Res **48**:47-54.

Dyerberg, J., H.O. Bang (1978). "Dietary fat and thrombosis." Lancet **1**:152.

Dyerberg, J., H.O. Bang (1979). "Haemostatic function and platelet polyunsaturated fatty acids in Eskimos." Lancet **2**:433-435.

Dyerberg, J., H.O. Bang, E. Stoffersen (1978). "Eicosapentaenoic acid and prevention of thrombosis and atherosclerosis." Lancet **2**:117-119.

Eaton, S.B., M. Konner (1985). "Paleolithic nutrition, A consideration of its nature and current implications." New Eng J Med **312**:283-289.

Fasching, P., K. Ratheiser, W. Waldhausl (1991). "Metabolic effect of fish-oil supplementation in patients with impaired glucose tolerance." Diabetes **40**:583-589.

Feskens, E.J.M. (1995). "Dietary factors determining diabetes and impaired glucose tolerance." Diabetes Care **18**:1104-1110.

Friday, K.E., M.T. Childs, C.H. Tsunehara, F.W.Y., E.L. Bierman , J.W. Ensinck (1989). "Elevated plasma glucose and lowered triglyceride levels from omega-3-fatty acid supplementation in type II diabetes." Diabetes Care **12**:276-281.

Glauber, H., P. Wallace, K. River, G. Brechtel (1988). "Adverse metabolic effect of omega-3 fatty acids in non-insulin-dependent diabetes mellitus." Ann Intern Med **108**:663-668.

Gramenzi, A., A. Gentile, M. Fasoli,E. Negri (1990). "Association between certain foods and risk of acute myocardial infarction in women." BMJ **300**(6727):771-773.

Harper, V., R. MacInnes, D. Campbell, M. Hall (1991). "Increased birth weight in northerly islands: is fish consumption a red herring?" BMJ **303** (Jul 20):166.

Hendra, T.J., M.E. Britton, D.R. Roper (1990). "Effects of fish oil supplements in NIDDM subjects." Diabetes Care **13**:821-829.

Holman, R.T., S.B. Johnson, P.L. Ogburn (1991). "Deficiency of essential fatty acids and membrane fluidity during pregnancy and lactation." Proceedings National Academy of Science USA **88**:4835-4839.

Innis, S.M., B.A. Lupton, C.M. Nelson (1994). "Biochemical and functional approaches to study of fatty acid requirements for very premature infants." Nutrition **10**(1):72-76.

Jensen, P.G., E. Nobmann (1994). What's in Alaskan Foods: Nutrition Services, Alaska Area Native Health Service, U.S. Department of Health and Human Services, Indian Health Service, Alaska Area Native Health Service: Chart Series.

Kromann, N., A. Green (1980). "Epidemiologic studies in the Upernavik District, Greenland." Acta Med Scand **208**:401-406.

Kromhout, D., E.B. Bosschieter, C.D.L. Coulander (1985). "The inverse relation between fish consumption and 20-year mortality from coronary heart disease." N Engl J Med **312**(19):1205-1209.

Landgraf-Leurs, N.M., C. Drummer, H. Froschl, S.R. (1990). "Pilot study on omega-3 fatty acids in type I diabetes mellitus." Diabetes **39**(3):359-375.

Lanting, C.I., V. Fidler, M. Huisman, B.C L. Touwen, E.R. Boersma (1994). "Neurological differences between 9-year-old children fed breast-milk or formula-milk as babies." Lancet **344**(Nov 12):1319-1322.

Lardinois, C.K. (1987). "The role of omega 3 fatty acids on insulin secretion and insulin sensitivity." Medical Hypotheses **24**:243-248.

Malasanos, T.H., P.W. Stacpoule (1991). "Biological effects of W-3 fatty acids in diabetes mellitus." Diabetes Care **14**:1160-1179.

Malcom, G.T., D.A. Boudreau, J.P. Middaugh (1996). Omega-3 fatty acids: gift from the sea. Tenth International Congress on Circumpolar Health, Anchorage, Alaska, American Society for Circumpolar Health: 255.

Martinez, M., A. Ballabriga, J.J. Gil-Gibernou (1988). "Lipids of the developing human retina: I. Total fatty acids, plasmalogens, and fatty acid composition of ethanolamine and choline phosphoglycerides." J Neurosci Res 20:484-490.

McManus, R.M., J. Jumpson, D.T. Finegood, M.T. Clandinin, E A. Ryan (1996). "A comparison of the effects of n-3 fatty acids from linseed oil and fish oil in well-controlled type II diabetes." Diabetes Care 19(5):463-467.

Middaugh, J.P. (1990). "Cardiovascular deaths among Alaskan Natives, 1980-86." Am J Public Health 80:282-285.

Middaugh, J.P. (1997). Cardiovascular Disease in Alaska: Alaska Division of Public Health: Epidemiology Bulletin No. 3.

Middaugh, J.P. (1997). Physical Activity and Health in Alaska: Alaska Division of Public Health: Epidemiology Bulletin No. 4.

Morris, M.C., J.E. Manson, B. Rosner, J.E. Buring, W.C. Willett, C.H. Hennekens (1995). "Fish consumption and cardiovascular disease in the Physician's Health Study: A prospective study." Am J Epidemiol 142(2):166-175.

Mouratoff, G.J., N.V. Carroll, E.M. Scott (1967). "Diabetes mellitus in Eskimos." JAMA 199:107-112.

Mouratoff, G.J., E.M. Scott (1973). "Diabetes Mellitus in Eskimos after a decade." J Am Med Assoc 226(11):1345-1346.

Murphy, N.J., L.R. Bulkow, C D. Schraer, A.P. Lanier (1993). "Prevalence of diabetes mellitus in pregnancy among Yup'ik Eskimos, 1987-1988." Diabetes Care 16(1):315-317.

Newman, W.P., G.T. Malcom, J.P. Middaugh (1996). Atherosclerosis and omega-3 fatty acids in Arctic populations. Tenth International Congress on Circumpolar Health, Anchorage, Alaska, American Society for Circumpolar Health: 297.

Newman, W.P., J.P. Middaugh, M.T. Propst, D.R. Rogers (1993). "Atherosclerosis in Alaska Natives and non-natives." Lancet 341(8852):1056-1057.

NIH (1995). Effects of Fish Oils and Polyunsaturated Omega-3 Fatty Acids in Health and Disease: bibliography 1995-A.

Nobmann, E.D. (1989). Dietary Intakes of Alaska Native Adults 1987-1988: Alaska Area Native Health Service: Final.

Norell, S.E., A. Ahlbom, M. Feychting, N.L. Pedersen (1986). "Fish consumption and mortality from coronary heart disease." Br Med J 293:426.

OBrien, J.S., D.L. Fillerup, J.F. Mean (1964). "Quantification of fatty acid and fatty aldehyde composition of ethanolamine, choline and serine phosphoglycerides in human cerebral gray and white matter." J Lipid Res 5:329-330.

Olsen, S.F., H.S. Hanson, T. I.A. Sorensen, B. Jensen, N.J. Secher, S. Sommer, L.B. Knudsen (1986). "Intake of marine fat, rich in (n-3) polyunsaturated fatty acids, may increase birthweight by prolonging gestation." Lancet ii(Aug 16):367-369.

Olsen, S.F., H.D. Joensen (1985). "High liveborn birthweights in the Faroes: a comparison between birthweights in the Faroes and in Denmark." J Epidemiol Community Health 39:27-32.

Olsen, S.F., J. Olsen, G. Frische (1990). "Does fish consumption during pregnancy increase fetal growth? A study of the size of the newborn, placental weight and gestational age in relation to fish consumption during pregnancy." International Journal of Epidemiology 19(4):971-977.

Olsen, S.F., J.D. Sorensen, N.J. Secher, M. Hedegaard, T.B. Henriksen, H.S. Hansen, A. Grant (1992). "Randomised controlled trial of effect of fish-oil supplementation on pregnancy duration." Lancet 339(8800):1003-1007.

Puhakainen, I., I. Ahola, H. Yki-Jarvinen (1995). "Dietary supplementation with n-3 fatty acids increases glugoneogenesis from glycerol but not hepatic glucose production in patients with non-insulin dependent diabetes mellitus." Am J Clin Nutr 61:121-126.

Raheja, B.S., S.M. Sadikot, R.B. Phatak, M.B. Rao (1993). "Significance of the N-6/N-3 ratio for insulin action in diabetes." Annals New York Academy of Sciences 683:258-271.

Sagild, V., J. Littauer, C.S. Jespersen, S. Anderson (1966). "Epidemiologic studies in Greenland 1962-1964. I. diabetes mellitus in Eskimos." Acta Med Scand 179:29-39.

Schmidt, E.B., J. Dyerberg (1994). "Omega-3 fatty acids. Current status in cardiovascular medicine." Drugs 47(3):405-24.

Schraer, C.D., A.P. Lanier, E.J. Boyko, D. Gohdes, N.J. Murphy (1988). "Prevalence of diabetes mellitus in Alaskan Eskimos, Indians, and Aleuts." Diabetes Care 11(9):693-700.

Scott, E.M., I.V. Griffith (1957). "Diabetes mellitus in Eskimos." Metabolism 6:320-325.

Shekelle, R.B., L. Missell, P. Oglesby, A.M. Shryock, J. Stamler (1985). "Fish consumption and mortality from coronary heart disease." N Engl J Med 313: 820.

Shekelle, R.B., J. Stamler (1993). "Fish and coronary heart disease: the epidemiologic evidence." Nutr Metab Cardiovasc 3:46-51.

Shkilnyk, A.M. (1985). A Poison Stronger than Love: The Destruction of an Ojibwa Community. New Haven, Yale University Press 275.

Siscovick, D.S., T.E. Raghunathan, I. King, S. Weinmann, K.G. Wicklund, J. Albright, V. Bovbjerg, P. Arbogast, H. Smith, L.H. Kushi, L.A. Cobb, M.K. Copass, B.M. Psaty, R. Lemaitre, B. Retzlaff, M. Childs, R.H. Knopp (1995). "Dietary intake and cell membrane levels of long-chain n-3 polyunsaturated fatty acids and the risk of primary cardiac arrest." J Am Med Assoc 274:1363-1367.

Storlien, L.H. (1996). "Skeletal muscle membrane lipids and insulin resistance." LIPIDS 31 (Suppl):S261-S265.

Storlien, L.H., A.B. Jenkins, D.J. Chisholm, W.S. Pascoe, S. Khouri, E.W. Kraegen (1991). "Influence of dietary fat composition on development of insulin resistance in rats. Relationship to muscle triglyceride and omega-3 fatty acids in muscle phospholipid." Diabetes 40:280-289.

Tinoco, J., P. Miljanich, B. Medwadowski (1977). "Depletion of docosahexaenoic acid in retinal lipids of rats fed a linolenic acid-deficient linoleic acid-containing diet." Biochem Biophys Acta 486:575-578.

Uauy, R., P. Peirano, D. Hoffman, P. Mena, D. Birch, E. Birch (1996). "Role of essential fatty acids in the function of the developing nervous system." Lipids 31:S-167 - S-176.

Uauy-Dagach, R., P. Mena (1995). "Nutritional role of omega-3 fatty acids during the perinatal period." Clinics in Perinatology 22(1):157-175.

USDA (1996). Food and Nutrition Center Web Site. US Department of Agriculture. www.nal.usda.gov.

USDA (1997). Nutrient Database. Release 11-1 (August 1997). Standard Reference. http://www.nal.usda.gov./fnic/.

Usher, P.J., M. Baikie, M. Demmer, D. Nakashima, M.G. Stevenson, M. Stiles (1995). Communicating About Contaminants in Country Food: The Experience in Aboriginal Communities: Research Department Inuit Tapirisat of Canada: ISBN 0-9699774-0-9.

Vollset, S.E., I. Heuch, E. Bjelke (1985). "Fish consumption and mortality from coronary heart disease." N Engl J Med 313:820-821.

Wheatley, B. (1994). "A new approach to assessing the effects of environmental contaminants on aboriginal peoples." Arct Med Res 53(2):386-390.

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Risks in Perspective - Methylmercury

Executive Summary

Mercury occurs naturally in the earth's crust, is ubiquitous in the environment, and has always been a component of freshwater and marine fish and mammals. Human industrial activities such as coal burning contribute to the global distribution of mercury into the environment.

Currently, there is good agreement worldwide regarding safe levels of dietary methylmercury intake for adults. Controversy exists, however, regarding the most appropriate guidelines for dietary intake of methylmercury to protect the developing fetus. Existing dietary intake guidelines are based upon the Minimata and Niigata, Japan poisoning outbreaks associated with heavily industrial mercury-polluted fish, and from the Iraqi mercury poisoning outbreak, where grain treated with a mercury fungicide and intended for seed was instead ground and used to bake bread. The World Health Organization (WHO) relied heavily upon these data to develop a provisional tolerable weekly intake (PTWI) for methylmercury of 230 μg and for total mercury of 300 μg. This weekly intake corresponds to a daily dose of 0.47 μg/kg/day.

Recently, the US Environmental Protection Agency (USEPA) developed a new reference dose (RfD, i.e., the dose that can be consumed daily over a lifetime without ill effects), for methylmercury that is 0.1 μg/kg/day, nearly one-fifth of the WHO intake guidelines. The new RfD would result in highly restrictive fish and seafood consumption advisories. For example, average fish total mercury (Hg) tissue concentrations of bass, crappie, dolphin, halibut, mackerel, pike, snapper, and tuna range from 0.2 to 0.3 ppm. For an average weight 60-kg adult woman, routine consumption of 4 ounces a week of fish containing average total mercury tissue concentrations of 0.25 ppm would provide the RfD for methylmercury exposure. Similarly, routine consumption of 1.9 pounds of fish or seafood a week that contained an average of 0.05 ppm total Hg (i.e., anchovy, butterfish, clams, herring, haddock, kingfish, mullet, salmon, silver hake, spotfish, squid, smelts, and trout), would provide the USEPA RfD.

Intake guidelines based upon the new USEPA RfD derived from the Iraqi event, however, may not be appropriate for calculating safe doses of methylmercury exposures that occur through the consumption of fish or marine mammals because of the following considerations:

- the Iraqi exposures were high-dose and acute;
- the study population, most likely, suffered from malnutrition;
- exposures included mercury compounds other than methylmercury;
- the small numbers of infant-mother pairs (n=30) at the low range of exposures in the Iraq study make risk modeling highly sensitive to derivations in statistical modeling approaches, so that

there is a wide range in the outcomes of risk assessment;

- mothers' recall of the timing of developmental milestones may not have been accurate when they were questioned several years after the poisoning episode;

- fungicide-treated grain is a very different exposure than low-level exposures to methylmercury through the consumption of fish and marine mammals which contain nutrients such as selenium, vitamin E, and other dietary factors that may protect against methylmercury toxicity.

In addition to the above considerations, the preponderance of epidemiologic information does not support the need for restrictive fish consumption advisories at low-levels of fish tissue concentrations. To illustrate, a recently published large-scale study of over 700 infant-mother pairs in the Seychelles identified no deleterious effects of heavy fish consumption: 75% of the women reported eating 10-14 fish meals per week.

Recent studies in the Faroe Islands, where methylmercury exposure is primarily through consumption of pilot whale meat, of 917 children evaluated at 7 years of age found no clinical or neurophysiological mercury-related abnormalities. Subtle decreases in some neuropsychological test results were found to be associated with low-level mercury exposure, although most test scores of highly exposed children were normal.

The impact of developing restrictive seafood consumption guidelines based upon the new EPA RfD, if adopted in Alaska, would be severe for subsistence fishing villages, sport fishing, tourism, and commercial fishing.

Because fish is a healthy and readily available food item that is high in protein, low in saturated fat, and a rich source of omega-3 fatty acids and antioxidants such as selenium and vitamin E, an exposure of potential risk (methylmercury), co-exists with nutrient exposures which provide health benefits. Severely limiting the consumption of fish or marine mammals will reduce health benefits and may have unintended or unforeseen negative health consequences. Thus, the evaluation of food safety and the development of food consumption advice must occur within a multidisciplinary public health framework.

For women of reproductive age, dietary intake of omega-3 fatty acids may be beneficial to the developing fetus and breastfed infant: omega-3 fatty acids are required for optimal central nervous system and retinal development and maturation of the visual cortex in human infants. Dietary intake of omega-3 fatty acids may also provide a protective role against the development of non-insulin dependent diabetes mellitus (NIDDM). Fish consumption has also been associated with reduced risk of cardiovascular morbidity in the general population and moderate, but not excessive, intake may be beneficial in reducing cardiovascular risk in NIDDM patients.

For subsistence populations with a heavy reliance upon fish, restrictive food consumption advisories could damage the social and economic infrastructure of entire villages and the health and well-being of community members. In Canada, detrimental changes in the health status of subsistence populations occurred following the social, economic, lifestyle, and dietary changes associated with fish consumption

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advisories. The health benefits of seafood and the changing patterns of disease noted in populations with changing dietary and lifestyle patterns are further reviewed in the chapter on the benefits of traditional food.

In order to provide sound advice regarding appropriate dietary guidelines for Alaska, we reviewed the toxicologic, epidemiologic, and risk assessment literature on methylmercury, and monitoring data on fish and marine mammals from Alaska and other arctic areas, and data from national surveys of market fish.

Recommendations and Future Directions

Because methylmercury is a known neurologic toxin, efforts to protect the environment by reducing industrial sources of mercury should be supported. In addition, efforts to reduce the acidification of lakes associated with acid rain may also be a worthwhile public health effort, since low pH levels in fresh water lakes may increase the methylmercury concentrations in fish. Inland waters may be particularly sensitive to mercury pollution, and geographic areas deficient in selenium may be especially vulnerable to the toxic effects of methylmercury in fish tissues. As new land use developments are being considered in Alaska, environmental impact statements need to carefully evaluate the potential impact of the proposed development on methylmercury concentrations in fish.

The preponderance of data suggests that low-level methylmercury exposures through fish and marine mammal consumption are not deleterious to neurodevelopment when dietary intake levels are comparable to existing WHO dietary intake guidelines. The Canadian experience suggests that the negative consequences of fish consumption

advisories are real and tangible while the benefits of advisories are uncertain and subject to considerable scientific debate. Fish and marine mammals provide an inexpensive and readily available source of nutrients, essential fatty acids, antioxidants, calories, and protein to Alaska residents and Native peoples and may provide health benefits such as protection against NIDDM, cardiovascular disease, and improved maternal nutrition and neonatal and infant brain development. Based upon the full range of information available, the Alaska Division of Public Health supports unlimited consumption of fish and marine mammals.

Because many scientific questions about mercury and subsistence diet exposures remain, the Alaska Division of Public Health recommends a coordinated and multidisciplinary research plan, outlined in the concluding remarks of this chapter.

Methylmercury

Background

Mercury is an element that occurs naturally in the earth's crust and is ubiquitous in the environment. All classes of rocks contain some amount of mercury ore, but the mineral cinnabar contains the greatest concentration, 86.2% mercury (Stokinger 1981). Mercury is dispersed throughout the environment through weathering processes, erosion, volcanic emissions, and off-gassing of the earth's crust. Mercury is methylated by micro-organisms in fresh and marine water and concentrated in fish and marine mammals.

Some of the human activities that result in the release of mercury into the environment

include coal burning, mining and smelting of mercury ores, and industrial emissions from factories using mercury in production processes. Incineration of garbage, including medical, agricultural and municipal wastes also releases mercury into the environment (ATSDR 1994).

Mercury has several chemical forms: elemental (metallic) mercury (a shiny, silver-colored liquid), inorganic mercury (white powders or crystals or red/black cinnabar); and organic mercury (mercury bound to carbon). Metallic mercury is refined from mercuric sulfide from cinnabar mines and is used in a variety of products: thermometers, batteries, electrical switches, and in the production of chlorine gas and caustic soda (ATSDR 1994). Methyl-mercury, a form of organic mercury, is created by microorganisms in fresh and salt water and soils that methylate inorganic mercury. There are a number of environmental factors that contribute to the methylation of inorganic mercury. For example, anaerobic conditions promote the methylation of mercury by sulfur-reducing bacteria (Gilmour et al. 1991); and low pH enhances the growth of yeasts, such as *Candida albicans* and *Saccharomyces cerevisiae* that methylate mercury (Yannai et al. 1991).

While the global distribution of mercury from industrial sources contributes to the burden of methylmercury in fish and marine mammals, the extent to which current tissue concentrations reflect natural or anthropogenic sources in Alaska is not known. Methylmercury has always been a component of fish and marine mammal tissue. Existing archeological data of ancient human and animal hair indicate lower levels of total mercury or methylmercury concentrations in the past

compared to modern-day concentrations. Data, however, are sporadic, consisting of a total of 18 ancient individuals representing various geographic locations and time periods in the circumpolar north (Toribara et al. 1984; Wheatley et al. 1988; Hansen et al. 1989). In Barrow, total mercury in hair was 4.8 ppm in a 25 year-old and 1.2 ppm in a 50-year-old mummy from the Barrow frozen family (Toribara et al. 1984). In Canada, 5th and 12th century hair MeHg levels ranged from 0.8 to 3.7 ppm with a mean level of 1.7 ppm among eight individuals (Wheatley et al. 1988). In Greenland, the mean total hair mercury level of 15th century mummies was 3.1 ppm among six adults and 10.00 ppm among 2 children (Hansen et al. 1989).

While current-day levels of hair MeHg or Hg may be comparable to the range observed in the ancient human hair specimens, analyses of ancient hair must be interpreted with caution. Studies directly comparing levels of pre-industrial and current-day mercury levels in animal species or humans from the same area clearly show increases in mercury levels over time. In Northern Baffin Island, for example, six archeological samples of polar bear hair showed MeHg concentrations ranging from 0.3 to 1.3 ppm with a mean level of 0.7 ppm while present day samples of hair from 7 polar bears from a location near the archeological site showed a mean level of 6.6 ppm (Wheatley et al. 1988). Animal fur and teeth have also been examined and show increases in mercury over time (Hansen et al. 1989; Eide et al. 1997). Also, total Hg measures in molars taken from moose from Isle Royale in Lake Superior, for example, increased from 135.0 ng Hg/g of tooth substance prior to 1966 to 253.7 ng Hg/g after 1970 (Eide et al. 1997).

Methylmercury in Marine Mammals and Fish

Methylmercury is taken up by fish in fresh and marine water. Because methylmercury has a long half-life in fish (about 2 years) (Stopford et al. 1975), it bioaccumulates in fish tissue and is biomagnified throughout the food chain, with piscivorous fish (fish that eat other fish) having higher methylmercury concentrations than non-piscivorous fish. Similarly, baleen whales which filter feed on plankton have considerably lower methylmercury exposures than toothed whales which feed on species higher in the trophic level of the food chain. In fish, most of the total body mercury is found in muscle as methylmercury (> 95%) (Bloom 1992). In marine mammals, which have the ability to demethylate mercury, total body mercury concentrations largely consist of inorganic mercury, at least in the liver (Smith et al. 1975; Born et al. 1981; Becker et al. 1995). Tables 1-3 depict a wide range in liver and kidney total mercury levels of marine mammals from published reports in Alaska and the arctic.

Only a few published studies examined both methylmercury and total mercury in liver and kidney tissues; based on the available data, only a small percentage of the total mercury in organ tissues is actually methylmercury. For example, in beluga whale, mean liver MeHg levels were 13.6% (1.03 mg/g) of the mean total mercury concentrations (22.01 mg/g) based upon MeHg and Hg measurements from 15 animals sampled from three locations in Alaska (NIST unpublished data, Becker, personal communication 10/10/97). In Greenland, the percentage of total mercury that was methylmercury in seal muscle tissue was 57-86%; however, the concentration of total mercury was low (Johansen 1981). Because inorganic mercury is regarded as a low potential health risk, clarification of both the ratio of methylmercury to total mercury and the amount of mercury in various tissues of different species is needed for a better assessment of the toxicological implications of heavy consumption of tissues of marine mammal species.

Limited data are available regarding the methylmercury content of fish in Alaska. In an analysis of fish from Kaiyuh Flats in West Central Alaska in 1993, methylmercury levels in 48 northern pike were low, ranging from 0.091 to 0.832 ppm wet weight, with a mean of 0.438 ppm (Headlee 1996). Limited sampling of fish and shellfish in Norton Sound also showed low mercury levels: 0.01 ppm in saffron cod, 0.02 ppm in least cisco, and 0.03 ppm in king crab (wet weight) (Rusanowski et al. 1987). In a study of fish in the Koyukuk Nowitna National Wildlife Refuge, northern pike muscle mercury tissue concentrations averaged 0.7 ppm, ranging from 0.07 to 2.9 ppm (U.S. Dept. of the Interior 1989). Of the 30 samples, 6 tested at or greater than 1 ppm, the action level set by the Food and Drug Administration. A 1993 salmon research project found very low tissue levels of methylmercury, with the highest level reported as 0.06 ppm among the 16 fish tested from Alaska waters (FDA et al. 1993).

Health Effects of Methylmercury

In 1953, an undefined central nervous system disease was first identified in Minamata, a chemical manufacturing city in Japan. By 1959, it was determined that the Minamata disease was associated with the intake of fish and shellfish from Minamata

Bay, and that mercury was the probable cause of the outbreak (Kutsuna 1968). In 1965, another outbreak occurred associated with the consumption of fresh water fish contaminated by mercury and methyl-mercury compounds that were discharged by a chemical plant into the Agano River in Niigata, Japan (Kinjo et al. 1995).

Another widespread mercury poisoning episode occurred in Iraq in the winter of 1971-1972, when over 6,000 people were hospitalized and 400 died from severe poisoning after consuming bread baked from mercury-fungicide treated wheat grain intended for planting (Bakir et al. 1973). Methylmercury was the predominant form of mercury found in the tested wheat. Minor amounts of ethylmercury were also detected in wheat, and a portion of the wheat may have been treated with the phenylmercuric compounds, ethylmercury-p-toluenesulfonanilide or N-dimethyl-mercury-p-toluene-sulfonamide (Bakir et al. 1973). However, these compounds were not detected in the wheat samples tested at the time of the outbreak. Barley shipments contained a more complex mixture of mercury compounds than the wheat: phenylmercuric acetate, methylmercury dicyandiamide, methylmercury-2,3-dihy-droxypropylmercaptide and methylmercury acetate (Bakir et al. 1973). The barley was not eaten but fed to animals and in the rural areas where the outbreak occurred, animal meats were consumed less than once weekly, while contaminated bread was eaten on a daily basis (Skerfving et al. 1976).

These outbreaks with extremely high exposures to mercury resulted in death for some and in severe, irreversible neurological damage for others. Milder forms of toxic effects were also noted.

Nervous system effects included personality changes such as irritability and nervousness, tremors, visual and hearing impairment, and memory loss. The mercury exposure, which interferes with brain development, resulted in central nervous system disease ranging from severe brain damage to milder forms of developmental deficits and delays, such as delayed walking and talking (Cox et al. 1989). In the Japan and Iraq episodes, the offspring exposed in utero to methylmercury showed greater signs of toxic effects than their mothers (Marsh et al. 1980; Marsh et al. 1981; Clarkson 1991). The most severe effects noted among those prenatally exposed were blindness, severe hearing impairment, and paralysis (Amin-Zaki et al. 1974). The most severely affected infants had extremely high blood levels [$\geq$3,000 parts per billion (ppb)] of total mercury. Based upon 81 infant-mother pairs from Iraq, maternal hair concen-trations above 70 μg/g (ppm) were associated with a 30% risk of abnormal findings in infants. High doses and long-term exposures to methylmercury can also damage the kidney, stomach and large intestine, sperm and male reproductive organs, and increase the number of spontaneous abortions and stillbirths.

Unlike cadmium and inorganic mercury, ingested methylmercury is readily absorbed (>95%), distributed throughout the body, and has an average biological half-life in humans of 70 days (Miettinen 1973). Thus, it is possible to calculate past or recent dietary intake in a population with biological exposure data, or vice versa. If the dietary intake is constant over time, then it is possible to calculate a steady state body burden. Thus, in stark contrast to ingested cadmium, a strong linear relationship has been demonstrated to exist between daily

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ingested methylmercury and the level of methylmercury in blood (Skerfving 1974; Clarkson 1977). More specifically, average dietary intake can be predicted as follows:

daily intake = (blood concentration [μg/L] x the elimination constant [0.014], x volume of blood in liters [5])/ (the absorption factor [0.95] x [fraction of uptake by blood [0.05] x body weight in kg) (USEPA 1996).

Also, hair mercury concentrations correlate with blood concentrations at the time of hair formation, with every centimeter of hair reflecting one month's growth and the average blood concentration during the month of hair formation (Al-Shahristani et al. 1976). While a general guideline for a hair:blood ratio is 250:1, ratios range widely from 140:1 to 370:1 (IRIS 1992 Integrated Risk Information System; USEPA 1995). Factors which may influence the hair:blood ratio are not established. The formula used to convert hair levels to blood concentrations is as follows: hair concentration (in ppm or mg/kg)/.25 = concentration in blood (micrograms per liter, μg/L; or ppb).

Methylmercury may produce its toxic effects through a variety of mechanisms which have been explored in laboratory and animal studies and are too numerous to review here (WHO 1990). In brief, methylmercury interferes with glutathione peroxidase activity (Hirota et al. 1980 2 references); inhibits protein synthesis in target nerve cells (Yoshino et al. 1966; Syversen 1982); interferes with myelin (Ganser et al. 1985) and mitochondrial DNA synthesis (Miller et al. 1985); and reacts directly with receptors in the nervous system, such as the acetylcholine receptor in peripheral nerves. Methyl mercury may also arrest the division of neurons during

brain development (Sager et al. 1982) perhaps through inhibition of the microtubular system by binding to free sulfhydryl groups on the surface and ends of microtubules (Vogel et al. 1985).

Background on the Scientific Information Upon Which Food Consumption Guidelines are Based

Dietary intake guidelines for methylmercury, the most common chemical form of organic mercury found in the diet, are based upon the knowledge gained from the acute poisoning episodes in Minamata and Niigata, Japan, and Iraq. These high-dose exposure incidents represent exposures qualitatively very different from the low-level methylmercury exposures associated with seafood consumption. For adults, the lowest detectable clinical effect of methylmercury poisoning is paresthesia (a numbness and tingling sensation) around the mouth, lips, fingers and toes. The lowest observed adverse effect level (LOAEL) for methylmercury was estimated to be about 220 ppb in whole blood (or 52 ppm in hair) based on the Japanese data, and 240-480 ppb in whole blood based upon the Iraqi data. It should be mentioned, however, that the Japanese data was analyzed by the dithizone procedure; a later reanalysis of the hair from the patient with paresthesia with the lowest hair mercury concentration (52 ppm), using the newer atomic absorption technique, yielded a value of 82.6 ppm (WHO 1990). All other affected individuals had hair levels above 100 ppm (Figure 1).

The WHO Provisional Tolerable Weekly Intake (PTWI) for total mercury is 300 μg and for methylmercury is 230 μg for a 70-kg person, or 0.47 μg/kg body weight per day (Tollefson et al. 1986). A consistent

intake of the WHO PTWI would correspond to a blood concentration of 20 ppb and hair mercury concentrations of 5 ppm. These exposure levels are one tenth of the LOAEL depicted in Figure 1.

The US FDA calculated the tolerance level for edible portions of seafood for interstate commerce by assuming an acceptable methyl mercury daily intake of 0.47 μg/kg body weight per day, a half pound (226 g) of fish consumed per week, and a 70-kg adult, resulting in a tolerance level of 1 ppm (1 ppm = [0.47 μg/kg x 7 days x 70 kg]/226 g of seafood consumption).

Because the developing fetus is more susceptible to methylmercury's effects than an adult, concern exists regarding whether the current guidelines are protective for in-utero exposures. Various approaches have been used to estimate a safe prenatal exposure level; most rely upon analyses of information from infant-mother pairs from the Iraq poisoning episode.

The Iraqi data, with 81 infant-mother pairs, has been examined in a variety of ways by different investigators and agencies to help determine the LOAEL for developmental toxicity using the endpoint of delayed walking (i.e., not walking by 18 months of age) (Cox et al. 1989). Exposures to methylmercury were assessed using sections of mothers' hair formed during pregnancy. Cox and colleagues conducted a dose-response analysis of the delayed walking data and concluded that the best estimate of a threshold effect on delayed walking was 10 ppm Hg in maternal hair, assuming no background frequency of delayed walking (Cox et al. 1989). The statistical analysis was based upon a "hockey stick" dose-response mathematical model (named after

the shape of the line) of delayed walking by exposure level. WHO concluded that a "prudent interpretation of the Iraqi data implies that a 5% risk may be associated with a peak mercury level of 10-20 μg/g (ppm) in the maternal hair" (WHO 1990).

The Iraqi data have been used in a number of different statistical models in attempts to provide a basis for setting guidelines for methylmercury exposure through fish consumption. Because of the small number of infant-mother pairs in the low range of exposures (approximately 30 infant-mother pairs had a maternal hair mercury concentration under 10 ppm), statistical models attempting to identify a threshold level of no adverse effects are particularly sensitive to assumptions of background frequency of delayed walking and to various derivations in the statistical modeling approaches (Crump et al. 1995).

In an USEPA reanalysis of the Iraqi data, a benchmark dose modeling approach was used combining the following data: delayed onset of walking, delayed onset of talking, mental symptoms, seizures, and neurological scores determined by clinical evaluation (USEPA 1996). The modeling approaches used (polynomial and Weibull models) predicted a benchmark dose of 11 ppm Hg in hair, interpreted as the hair level corresponding to a 5% chance of a 10% increased risk level associated with MeHg exposure. The benchmark dose (11 ppm maternal hair), which corresponds to a daily intake of 1.1 μg/kg/day was divided by an uncertainty factor of 10 to provide the new reference dose (RfD) of 0.1 μg/kg/day (USEPA 1996) (i.e., nearly one-fifth the tolerable intake proposed by the Joint FAO/WHO).

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In rodents, intake of 10 μg/kg/day resulted in a slight reduction in the rate of pressing on a lever to receive a reinforcement (Bornhausen et al. 1980): dividing this dose by 100 (10 for the uncertainty factor x 10 for the modifying factor for extrapolating from animals to humans) provides the same RfD of 0.1 μg/kg/day (Gilbert et al. 1995). The new RfD would correspond to a new tolerance level for seafood concentrations of MeHg of 0.2 ppm (0.2 ppm = [0.1 μg/kg x 70 kg x 7 days]/226 grams per week).

The new tolerance level is being used by some states to issue fish consumption advisories to subsistence and sport fish consumers. It should be mentioned, however, that ubiquitous background levels of methylmercury in certain species of fish routinely exceed the tissue concentrations determined to be "safe" using the new RfD. The US FDA uses 1 ppm of methylmercury as the cut-off level for interstate commerce. Certain species of fish available in the market would be subjected to a fish consumption advisory in states using the new USEPA RfD.

It should be mentioned that all of the statistical modeling above and the resulting dietary intake guidelines relies on the Iraqi data. Because the date of birth of the 81 infants studied was not known, the month of birth was determined by mothers' recall of birth relative to its relationship to the poisoning event and recall of age at time of first walking (Marsh et al. 1987). A large percentage of the values of age at time of walking recalled by mothers and family members were given in even multiples of 6 months, suggesting that recall data may only be accurate within a margin of error of about 6 months (Crump et al. 1995). Also,

interviews were conducted with the mothers several years after the poisoning incident.

While much has been learned from the Iraqi poisoning episode, a number of considerations suggest that the Iraqi data may not be appropriate for calculating safe doses of low-levels of methylmercury exposures through consumption of fish or marine mammals. The high-dose and acute nature of the Iraqi exposures, the likelihood that the study population suffered from malnutrition, the fact that prenatal exposures may have also included other mercury compounds, the apparent uncertainty of the major outcome variable (age at time of first walking), and the small numbers of infant-mother pairs at the low-range of exposures suggest that the Iraqi data may not be appropriate for determining acceptable chronic low-level exposures to methyl-mercury through fish consumption.

Other Epidemiologic Studies of Methylmercury Exposure and Effects

Several populations exposed to methyl-mercury through fish consumption have also been studied. In Sweden, families with blood levels of Hg up to 60 ppb had no signs or symptoms of mercury poisoning (Skerfving 1974). In a group of fishermen in American Samoa who ate fish daily for 22 months, no evidence of methylmercury poisoning was observed: the average blood concentration was 64 ppb. These data suggest that the current acceptable methylmercury daily intake of 0.47 μg/kg/day (which would correspond approximately to a blood methylmercury level of 20 ppb) is not harmful, at least for the adult population.

Several attempts have been made to characterize the risks of prenatal methylmercury exposure in fish consumers. In a Peruvian study of 131 infant-mother pairs, with peak maternal hair MeHg levels ranging from 1.2 to 30.0 ppm and a geometric mean of 8.3 ppm, no neurodevelopmental abnormalities were noted in the offspring (Marsh et al. 1995). Among 234 Cree Indian Children age 12-20 months from northern Quebec, Canada, mean maternal hair concentrations during pregnancy were 6 ppm; 6% had hair levels above 20 ppm. In boys, but not girls, abnormal muscle tone or reflexes were observed in 5 out of 13 (38.5%) boys in the highest exposure category of maternal hair mercury concentrations (13-24 ppm). No consistent dose-response was observed, however, by exposure category: among the 97 boys, the percentages with abnormal muscle tone or reflex were 15.8%, 5.6%, 26.3%, 0%, 7.1% and 38.5% from lowest to highest prenatal exposure category (McKeown-Eyssen et al. 1983). All other neurological test results were not associated with methylmercury exposure. Thus, this study appears to be a negative one (Marsh et al. 1995).

Children exposed in-utero to MeHg were also studied in New Zealand, where the dietary intake of MeHg is considered to be 3-4 times higher than the WHO PTWI in selected populations due to the high consumption of shark meat (Kjellstrom et al. 1989). Of over 10,000 women interviewed, 935 indicated that they ate fish more than three times per week, and of these women, 73 had maternal hair mercury levels above 6 ppm. Sixty-one of the children were available at six years of age for testing and compared to children with lower exposures: < 6 ppm maternal hair

levels. The data from the study did not show a strong association between prenatal mercury exposure and deficits in the psychological test scores. For 15 children who had mothers with average hair mercury concentrations above 13 ppm and peak segmental hair levels of 25 ppm during any one month of the pregnancy, poorer test performance for some of the measures were noted (i.e., test of language development, and the Weschler Intelligence Scale for children, Revised). The effect of mercury was small, however, compared to other influences such as social class and ethnic group. While the Cree and New Zealand studies are suggestive of a possible MeHg effect, the ability to rule out confounders and the influence of outliers in these small-scale studies is limited, and observations may be attributed to chance (WHO 1990).

Two Large-Scale Epidemiologic Studies on Prenatal Methylmercury Exposure

Because of the small size of the Cree, New Zealand, and Peruvian populations, two large-scale epidemiologic studies were designed to help quantify whether subtle neurodevelopmental effects are associated with chronic low-level in-utero exposures. One study took place in the Seychelle Islands off the coast of Africa and the other in the Faroe Islands in the North Atlantic between Scotland and Iceland. Because of the large sample sizes and the homogeneous nature of both study populations, the studies provide the best opportunity to characterize the magnitude and nature of the risks that may be associated with low-level methylmercury exposure through fish and/or marine mammal consumption. Because of the many caveats in extrapolating methylmercury risks from the contaminated grain episode in Iraq, the Seychelles and

Faroe Island studies are of particular relevance in the process of developing food consumption advice.

The Seychelles

The University of Rochester in collaboration with the Seychelles Island Government initiated a large scale study (the Seychelles Child Development Study) in which the developmental effects of low-level MeHg exposure through heavy fish consumption were examined in over 700 women (Cernichiari et al. 1995; Davidson et al. 1995; Marsh et al. 1995; Myers et al. 1995 Summary; Shamlaye et al. 1995). Seventy-five percent of the women indicated eating 10-14 fish meals per week (Shamlaye et al. 1995). Mercury levels in 20 different species of fish ranged from 0.001 ppm for reef fish to 2.04 ppm for Moro Shark, and 4.4 ppm for Dog Tooth Tuna (Cernichiari et al. 1995). Multiple maternal hair samples were collected during pregnancy for quantification of MeHg exposures. Maternal hair mercury levels were as high as 36 ppm with a median of 6.6 ppm. There were strong correlations between maternal hair Hg levels between each trimester and the entire gestational period, indicating no seasonal differences or peak exposure periods that deviated from the average concentration during pregnancy.

Numerous neurodevelopmental tests and physical exams were conducted on the children at 6.5, 19, 29, and 66 months of age. The 66 months of age results are not yet available. The neurologic evaluation included the Fagan Test, the Revised Denver Development Screening Test, the Bayley Scales of Infant Development, the General Cognitive Index, the Infant Behavior Record, Mental Developmental Index, McCarthy Scales of Children's Abilities, Psychomotor Developmental Index, Preschool Language Scale, and numerous other perceptual, verbal, memory, behavior and motor tests. Physical examinations were also conducted.

The recently published findings indicated no observed deleterious effects among the offspring born to the heavy fish consuming women in the population. For example, the neurological examination of offspring identified results that were similar for each category of exposures corresponding to maternal hair mercury levels: 0-3 ppm, 3-6 ppm, 6-9 ppm, 9-12 ppm, and > 12 ppm in maternal hair (Myers et al. 1995 Pilot Study) (Figure 2). The Revised Denver Developmental Screening Test (DDST) identified only 3 abnormal test results and the prevalence of normal findings were similar across all exposure categories, with a slightly, but not significantly, greater percentage of children in the highest exposure category having a questionable test result (Figure 3).

Although maternal hair concentrations ranged as high as 36 ppm, all but two women in the study had hair concentrations under 20 ppm, and 659 (80% of the cohort) had maternal hair concentrations less than or equal to 12 ppm. Thus, the Seychelle study is not able to definitively address the extent of risks at the high end of exposures observed in this population. However, the data provide an extensive and exhaustive look at a variety of outcomes and provide compelling evidence that the current WHO guidelines, which correspond to hair mercury levels of 5-6 ppm, are protective of in-utero exposures to MeHg through heavy fish consumption.

The Faroe Islands

The other large-scale study took place in the Faroe Islands (Grandjean et al. 1994). Evaluation of the possible in-utero neurologic effects was made using neurologic and developmental tests conducted at 2, 5, and 7 years of age. Of 1,023 consecutive births, the median umbilical cord blood-mercury concentration was 24.2 μg/L (ppb); 25.1% (n=250) had blood-mercury concentrations that exceeded 40 μg/L. The median maternal hair mercury concentration was 4.5 ppm, with 12.7% (n=130) of the women having concentrations exceeding 10 ppm (Grandjean et al. 1992). In early results, no adverse effects of MeHg were detected (Grandjean et al. 1995).

A follow-up analysis was conducted on the children at 7 years of age. Tests included the DDST, the Neurobehavioral Evaluation System (NES) finger tapping test, the NES Hand-Eye Coordination test, the Boston Naming Test for language skills, the WISC-r Block Designs and Bender gestalt test for visuospatial skills; and the Tactual Performance Test and California Verbal Learning Test for memory.

In the Faroe Islands, where MeHg exposure occurs primarily through consumption of pilot whale meat, analyses of 917 children at 7 years of age found no clinical or neurophysiological Hg-related abnormalities. However, subtle decreases in neuropsychological test performance were associated with prenatal Hg exposure at maternal hair levels below 10 ppm, "although test scores obtained by most of the highly exposed children were mainly within the range seen in the rest of the children..." (Grandjean et al. 1997). The long-term predictive value of these findings is not known, and the generalizability of these data to fish consumers is questionable. Interestingly, the Faroese children had excellent visual contrast sensitivity that may be attributed to the ample supply of dietary omega-3 fatty acids.

Other than the Faroe Island Study, the epidemiologic information on the effects of prenatal MeHg exposures in fish eating populations suggest that the WHO guidelines are protective for the developing fetus. The implications of exposures two times greater than the WHO guidelines (i.e., greater than 12 ppm maternal hair) are not as well characterized because of the relatively small number of study participants at the high range of exposures in the fish eating populations.

Animal Studies

Most rodent studies have examined very high levels of in-utero MeHg exposures (see attached references in (Buelke-Sam et al. 1985; Geyer et al. 1985; Inouye et al. 1985). In one often cited low-dose rodent study, no effects were observed in rodents dosed at 5 μg/kg/day, whereas 10 μg/kg/day was associated with a very slight and 50 μg/kg/day was associated with a significant reduction in the rate of pressing on a lever for a specified number of times to receive a reinforcement (Bornhausen et al. 1980). The division of 10 μg/kg/day by 100 (UFxMF) provides an RfD of 0.1 μg/kg/day (Gilbert 1995). Thus, from a conservative regulatory risk assessment approach, this animal study is supportive of USEPA's RfD based upon the Iraqi data. The Bornhausen rodent study, however, is highly unusual and not supported by all other laboratory rat studies (Stern 1993). Dosages associated

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with the lowest effect level in other rodent studies range from 50 to 500 times higher than the dosage in the Bornhausen study (Clarkson, personal communication 9/3/97).

In-utero exposures to MeHg have also been examined in other species such as mice and primates, but effects were not noted at such low doses as the Bornhausen study. Dosages were high in studies of non-human primate infants (Macaca fascicularis monkeys): 50, 70, and 90 μg/kg/day during pregnancy, resulting in average maternal blood MeHg levels of 1,280, 1,620, and 2,030 ppb, respectively(Burbacher et al. 1986; Gunderson et al. 1986; Gunderson et al. 1988; Burbacher et al. 1990). These high-dose exposures were related to delays in cognitive milestones, such as deficits in visual recognition memory, abnormal social behavior, and delayed attainment of object permanence. In a follow-up of the same monkeys tested as adults (7-9 years of age), no long-term deficits in spatial memory were noted in the monkeys that had in-utero exposures to MeHg (Gilbert et al. 1993). In fact, exposed monkeys made significantly more correct responses, fewer errors, and fewer delayed responses than control monkeys (Gilbert et al. 1993). In another follow-up evaluation of the adult monkeys (tested at 8-10 years of age), minor alterations in temporal discrimination were noted, and the effects appeared to be sex-specific: exposed females showed poorer temporal discrimination than non-exposed females, and exposed males performed better on selected tests than the unexposed controls (Gilbert et al. 1996). The adult data suggest that either some of the early developmental tests are not predictive of adult functioning or that the brain has the ability to compensate for some of the early deficits noted in these experiments.

In a Canadian study, monkeys exposed to MeHg at 25 or 50 μg/kg/day, either in-utero or postnatally to adulthood (up to 7 years of age), showed slight MeHg effects for visual, auditory and somatosensory function (Rice et al. 1982; Rice 1992; Rice et al. 1993). In a follow-up of these monkeys, motor and somatosensory deficits were noted in adulthood (Rice 1989).

While these studies are of interest in delineating possible neurodevelopmental sequelae associated with prenatal or postnatal methylmercury exposures, the dosages are considerably higher than those that occur through fish and seafood consumption and are, therefore, of limited value in predicting low-dose effects of methylmercury through the diet.

Dietary Intake and Risk Assessment

Available MeHg or total mercury monitoring data of subsistence species plus dietary intake data among subsistence users indicate that the WHO's provisional tolerable weekly intake of 300 μg for total mercury or of 230 μg for MeHg may be exceeded by a significant proportion of the population in the Faroe Islands (Weihe et al. 1996), Northern Greenland (Hansen 1990), and among the Inuit of Baffin Island, Canada (Chan et al. 1995).

For Alaska, little dietary intake data are available. However, it is very likely that a sizable portion of the Alaska population eats fish and shellfish several times a week, particularly during fishing season. In a dietary survey of Alaska Natives, fish ranked high in the list of frequently eaten foods (Nobmann et al. 1992). Among all seafood, salmon ranked highest in the species most often consumed. The mean of

the daily intake of shellfish and fish for Alaska Natives was 109 g (i.e., 3.82 ounces) compared with a 17 g average for the participants in the National Health And Nutrition Examination Survey (NHANES) II: a greater than 6-fold higher fish intake among Alaska Natives than national consumption estimates.

We calculated the allowable amount of different seafood products that could be consumed for an average weight 60-kg woman of reproductive age based upon USEPA's MeHg RfD, and the WHO's MeHg PTWI (Table 4). Fish Hg tissue concentrations from national surveys (Lowe et al. 1985; Stern 1996) were utilized for the calculation of average allowable consumption. If we assume average Hg tissue concentrations of 0.25 ppm (average Hg concentrations range from 0.2 to 0.3 ppm in national surveys for bass, crappie, dolphin, halibut, mackerel, pike, snapper, and tuna) routine consumption of 4 ounces a week of any of these seafood items would provide the USEPA RfD. WHO guidelines would correspond to an average weekly intake of nearly 2 pounds of the above mentioned seafood items. If we assume average Hg tissue concentrations of 0.05 ppm (anchovy, butterfish, clams, herring, haddock, kingfish, mullet, salmon, silver hake, squid, smelt, spotfish, and trout), routine consumption of 1.9 pounds a week of any of these seafood items would provide the USEPA's RfD. In contrast, the WHO guidelines would correspond to an average weekly intake of 9.3 pounds (Table 4). The epidemiologic literature from the Seychelles would suggest that considerably more fish could be safely consumed.

For marine mammals, there is incomplete information in the literature regarding the proportion of total mercury that is methylmercury. Unlike fish, marine mammals demethylate mercury. For species in which only total mercury concentrations are known, we assumed that 80% of total Hg is MeHg for marine mammal muscle and blubber tissue and that 3% of total Hg in liver tissues is MeHg. For bowhead whale, which filter feed on plankton, unlimited quantities of muscle (0.002 ppm Hg), blubber (0.005 ppm Hg) or liver organs (0.04 ppm Hg or an estimated 0.014 ppm for MeHg) could be consumed based upon USEPA's RfD or WHO's PTWI. For beluga, MeHg concentrations in blubber (0.08 ppm total Hg or an estimated 0.06 ppm for MeHg), muscle (0.7 ppm total Hg or 0.56 ppm MeHg) and liver (28.0 ppm Hg or 0.84 ppm MeHg) are below FDA's tolerance level of 1 ppm MeHg that is used for commercial seafood products. Table 4 provides average consumption guidelines for comparable levels of MeHg in seafood products.

Because fish and marine mammals are nutritious food items and because negative changes in health status have been observed in populations who have experienced food consumption advisories and resulting social and economic changes (Shkilnyk 1985), the need for and implications of issuing food consumption advisories based upon the WHO PTWI or the USEPA RfD must be carefully examined in context of the magnitude and implications of the benefits of consuming these food items and in context of the magnitude of error in extrapolating risks and exposures from tissue concentrations. (Egeland 1997)

Nature of methylmercury exposure through the ingestion of fish and marine mammals

Unlike the Japanese fish poisoning episodes and the Iraqi bread outbreak upon which the dietary guidelines are based, methylmercury exposures through the arctic food chain represent chronic low-level exposures. Dietary factors which are associated with methylmercury in fish and marine mammals may play an important role in methylmercury's toxicity and absorption. For example, mice fed methylmercury chloride with cod liver oil absorbed significantly less methylmercury than a comparison group of mice fed coconut oil or soy oil. (Hojbjerg et al. 1997). Also, high amounts of soy and fish protein reduced methylmercury absorption compared to low protein diets in the laboratory mice (Hojbjerg et al. 1997).

Also, a number of dietary factors may modify methylmercury's toxicity. Vitamin E, for example, may be an important dietary component that modifies methylmercury toxicity. Vitamin E is a well-known antioxidant and may provide protection against methylmercury's toxic effects on biological membranes through the prevention of membrane degradation (Chang et al. 1978). In studies of quails and rats, vitamin E improved growth rates and increased life span compared to animals exposed to methylmercury alone (Welsh et al. 1976). Also, vitamin E protected nervous tissue (in vitro) from the toxic effects of methylmercury (Kasuya 1975). In another study, hamsters fed vitamin E with methylmercury chloride showed none of the morphological signs of toxicity on nervous system tissues (such as neuronal necrosis in the cerebellum and calcarine cortex) that

were observed in hamsters fed methylmercury chloride alone (Chang et al. 1978).

Fish is a good source of vitamin E compared to other sources of animal protein. Salmon steak contains 1.8 mg/100g of vitamin E (measured as total tocopherols), shrimp (frozen, baked) contains 6.6 mg/100g, scallops (frozen, baked) contains 6.2 mg/100g, and haddock filet (broiled) contains 1.2 mg/100g of vitamin E (Bauernfeind 1980). In contrast, other dietary sources of protein contain lower levels of vitamin E: bacon (0.59 mg/100 g), bologna (0.49 mg/100 g); salami (0.68 mg/100 g); and chicken (0.58 to 1.39 mg/100 g)(Bauernfeind 1980).

Vitamin C may also be an important component of the diet that may modify methylmercury toxicity. Guinea pigs on a vitamin C deficient diet suffered more neurological damage when exposed to methylmercury than a comparison group of guinea pigs fed a diet with adequate vitamin C (Yamini et al. 1984). Thus, numerous dietary factors may play a role in reducing methylmercury toxicity.

Selenium

Levels of selenium (Se) within the range of nutritional requirements for dietary Se may be highly effective in reducing the toxicity of methylmercury (Ganther et al. 1972). One of the most notable early experiments found that Japanese quail given methylmercury in diets containing 17% tuna survived considerably longer than quail given the same amount of methylmercury (which was lethal) in a corn-soya diet (Ganther et al. 1972). The selenium content

of tuna was thought to protect the quail from MeHg toxicity. Since that study, many reports are available describing the antagonism between selenium and mercury (Stillings et al. 1972; Potter et al. 1973). For example, in a rat feeding study, all rats given mercury in their drinking water without a selenium supplement died at the end of a 6-week feeding study, while those fed mercury with selenium survived. In another study, sodium selenite protected offspring of mice from the neuro-developmental effects on reflexes observed with methylmercury exposure alone (Satoh et al. 1985).

The mechanisms by which selenium protects organisms from methylmercury toxicity are not fully understood. Substantial evidence suggests that selenium actually enhances whole body retention and accumulation of methylmercury in the brain (Stillings et al. 1974; Chen et al. 1975; Ohi et al. 1975; Magos et al. 1977; Alexander et al. 1979; Magos et al. 1987; Hansen 1988). It should be noted, however, that the form of selenium appears to influence the organ distribution and speciation of mercury in animal studies: administration of inorganic selenite with Hg resulted in a greater proportion of total mercury in tissues than after a dose of organic selenium (Magos et al. 1984). Various mechanisms may play a role in selenium's protective effect against metal toxicity. Some hypothesize that selenium's protective effect is attributed to selenium and mercury forming a biologically inactive compound (Groth et al. 1976; Naganuma et al. 1981; Magos et al. 1987; Hansen 1988). However, since small amounts of Se are protective against larger amounts of Hg, others suggest that the magnitude of protection is probably explained by other mechanisms (Ohi et al.

1980), such as selenium's ability to protect neuronal tissues against methylmercury toxicity through its role in the antioxidative process (Chang et al. 1982). Evidence for this mechanism comes from the finding that rats fed MeHg for six weeks showed a marked suppression in glutathione peroxidase (GSH-Px) activity, while rats exposed to both MeHg and Se showed no significant alteration in GSH-Px activity (Chang et al. 1982).

While the literature is promising, it is not conclusive. Further work is needed to better characterize the extent to which selenium is protective of methylmercury toxicity at dosages commonly found in fresh and salt water fish. Selenium at high doses is in itself toxic and some discrepancies in the protective effect of selenium-mercury feeding studies may be, in part, attributed to the relatively high levels of selenium and mercury used in the animal studies. Also, selenium's half-life is considerably shorter than that of MeHg and may help explain why in some studies Se's protective effect disappears over time in high dose MeHg feeding studies.

The concentration of Se in unpolluted ocean waters is under 1 μg/L (Ihnat et al. 1989). Selinium in the earth's crust is not uniformly distributed, however, and some geographical areas have deficient amounts of Se in soil and plant life (ATSDR 1994). Marine fish and mammals accumulate selenium through the food chain, while crustaceans absorb selenium directly from water and sediments (Ihnat et al. 1989). In general, selenium concentrations in marine fish, shellfish, and marine mammals are higher than those found in terrestrial animals or fresh water fish (Ihnat et al. 1989). Marine fish contain average

selenium concentrations ranging from 0.4 to 0.9 ppm in most species (Hall et al. 1978).[1]

The liver and kidney tissues of marine fish and mammals and the hepatopancreas of shellfish usually contain the greatest concentrations of selenium (Guinn et al. 1974; Grieg et al. 1976; Chou et al. 1978; Shultz et al. 1979; Luten et al. 1980; Wrench et al. 1981).

In marine mammals and in some studies of marine fish, mercury and selenium accumulate in livers and kidneys in a one-to-one molar ratio (Ganther et al. 1972; Koeman et al. 1975; MacKay et al. 1975; Kari et al. 1978; Shultz et al. 1979; Tamari et al. 1979; Ganther 1980). In contrast to marine mammals, in most marine fish, selenium concentrations are usually several times higher than those of mercury (Freeman et al. 1978; Cappon et al. 1981; Cappon et al. 1982; Ihnat et al. 1989). Fish exposed to Hg polluted waters, however, contain considerably more Hg than Se (a 10:1 ratio), indicating that in areas of environmental pollution the uptake of Hg exceeds that of Se (Beijer et al. 1978). Table 5 depicts the selenium liver and kidney tissue concentrations summarized from the published literature on Alaska and other arctic marine mammal species (Ponce et al. 1996).

Inorganic vs. Organic Mercury in Liver Tissues

Liver and kidney of marine mammals can contain relatively high levels of mercury, the majority of which is inorganic. While it may be possible for inorganic mercury to be methylated by intestinal bacteria in humans (Rowland et al. 1975), this is not thought to happen to a large extent because inorganic mercury is readily excreted. In a laboratory study, cats fed ringed seal liver showed no neurologic or histopathologic abnormalities associated with mercury exposure, while cats fed beef liver plus methylmercury chloride developed the neurologic and histologic signs of mercury toxicosis within 90 days (Eaton et al. 1980). The total mercury intake from the seal liver was quite high (up to 158 mg over 90 days), while the total mercury intake from the beef liver with methylmercury chloride exposure group was lower (80-90 mg). Only a small percentage of the total mercury in the seal liver was organic, 3%. Tissue accumulation of mercury in the tissues of the cats reflected the organic fraction and not the high inorganic fraction of total mercury in the seal liver. Selenium levels in the liver and kidney of the cats fed ringed seal liver indicated that selenium levels increased with increasing levels of methylmercury. This was not observed in the cats fed beef livers with methylmercury chloride.

Studies on Human Exposures in Alaska

Because many factors influence the accuracy of risk assessments based upon fish tissue concentrations, hair or whole blood mercury concentrations can better quantify the levels of exposures in a population. Because of the high level of fish consumption in Alaska, several small studies have been conducted which examined human exposures to dietary methylmercury. A total of four different studies have been conducted: two in the Pribilof Islands, one in the Yukon-Kuskokwim Delta area, and one in Nome (Table 6). Generally these

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[1]Interestingly, selenium is not evenly distributed within a given tissue specimen. Thus, multiple sampling and sample homogenization is important in characterizing tissue concentrations.

studies have small sample sizes and efforts to characterize dietary intake of those tested were minimal or non-existent. The Centers for Disease Control conducted a study of mercury exposure among residents of the Pribilof Islands in 1970 (Hochberg et al. 1972). Analysis of hair or blood for mercury was performed on 48 residents, 34 of whom had hair mercury concentrations examined. Mean hair total mercury content was not found to be different among Alaska Natives eating fur seal liver at least once a week in 1970 (5.6 μg/g, n=15), Natives who did not eat liver (4.9 μg/g, n=13) and whites who did not eat liver (3.4 μg/g, n=6). The presumed high inorganic mercury content of mercury in liver (relative to methylmercury) may account for the lack of a significant difference in hair mercury concentration between consumers and non-consumers of fur seal liver. The highest hair mercury level (16.2 μg/g) was found in a resident of the Pribilof Islands in 1970.

The Alaska Department of Health and Social Services conducted an investigation of 145 Alaskans to determine whether exposure to mercury through the diet posed a potential health hazard in 1972 (unpublished report). Total mercury was determined in red blood cells, plasma and hair. Of the 130 that had hair measurements taken, mean mercury values in the hair of Pribilof Island residents (n = 13) was found to be 4.5-5.8 μg/g, while the average hair mercury concentration of new mothers in Bethel was 5.1 μg/g (n = 48). These concentrations were higher than those found in Juneau (1.5 μg/g, n = 8) and in villages along the Yukon and Kuskokwim Rivers (0.7-1.4 μg/g, n = 61). No overt signs of toxicity to the study population were observed.

A study of maternal-infant pairs for mercury exposure was conducted in the mid-1970s (Galster 1976). Hair, milk and blood from 38 mother-infant pairs from the Yukon-Kuskokwim coast and interior, and from Anchorage were analyzed for mercury. Of the 22 that had maternal hair measurements taken, results demonstrated no difference in hair mercury content between the coastal (4.3 μg/g, n=12), interior (3.6 μg/g, n=6) and urban (4.0, n=4) areas. Maternal and child plasma mercury levels did show a trend, however, with the highest mercury content in the coastal group, and the lowest content in the Anchorage group. For example, mean maternal mercury levels measured in red blood cells were significantly higher in the coastal area (33.5 ng/ml, n=17), when compared to the interior (22.6 ng/ml, n=11), and urban (8.9 ng/ml, n=10) areas. Other parameters, such as infant birth weight and Apgar scores were not significantly different by geographic area.

A study of 200 samples from women of child-bearing age in Nome from September to October, 1989 evaluated total hair mercury (Crecelius et al. 1990). This study found low mercury content in the hair (average = 1 μg/g, range 0.02-8.0). Only 12 samples were above 3.0 μg/g mercury in hair. A follow-up study conducted segmental analysis of hair from 80 Nome women obtained in the fall of 1990 (Lasorsa et al. 1991). This study also found low mercury levels in the hair of the Nome women. Unfortunately, no attempt was made to characterize dietary intake of fish and marine mammals in the women participating in the study. However, it was reported that 53 of the 80 participants were heavy subsistence food consumers (Lasorsa et al. 1991).

In general, hair or blood mercury concentrations observed in Alaska have been lower than what has been anticipated based upon tissue mercury concentrations and the frequency of fish and marine mammal consumption. Reasons for this discrepancy are unknown. However, the laboratory mice studies in Denmark showing reduced absorption of methylmercury when co-administered with cod liver oil or high protein diets suggests that the science of methylmercury is still emerging. The Alaska Native diet is both high in fish and marine oils and animal protein. The newly emerging research emphasizes the importance of gaining information specific to the dietary conditions of the arctic.

The data available suggest that exposure levels to methylmercury in Alaska, are, for the most part, below or near the WHO intake guidelines. Periodic screening programs could be conducted in Alaska to better characterize exposures in all geographic areas of the state.

Summary

Methylmercury is a known neurological toxin. Thus, efforts to reduce mercury in the environment from industrial sources should be supported in order to reduce the amount of mercury available for methylation and incorporation into the fresh water and marine food chain. Inland waters may be particularly sensitive to mercury pollution. Geographic areas deficient in selenium may pose increased risk from toxic effects of methylmercury accumulation in fish tissues. Acid rain from industrial pollution lowers the pH of fresh water lakes and may increase methylmercury concentrations in fish. As new land use developments are considered in Alaska, environmental impact statements need to carefully evaluate the potential impact of the proposed development on methylmercury concentrations in fish. This is particularly important for inland watersheds with selenium deficient soils.

The WHO PTWI and USEPA guidelines for methylmercury exposures are based upon the information gained from the outbreaks in Minamata and Niigata, Japan and in Iraq, which represent exposure scenarios substantially different from those of ubiquitous low-level methylmercury exposures through fish and marine mammal consumption. In the marine food chain in non-polluted areas, methylmercury bioaccumulates with selenium, which may protect against methylmercury's toxic effects. Other characteristics of the marine diet may also play a role in modifying methylmercury's toxicity and absorption. Information from high fish consuming populations in uncontaminated areas, such as the Seychelle Islands, suggest that substantial quantities of fish can be safely consumed.

Because many scientific questions about mercury and the subsistence diet remain, the Alaska Division of Public Health recommends the following research to help provide the information needed for the ongoing evaluation of the safety of marine mammal and fish consumption in Alaska:

- periodic screening for MeHg exposure through whole blood or hair analyses, particularly among women of reproductive age and among high consumers of fish and seafood in different geographic areas of the state;
- characterize differences between pre-industrial mercury and current-day mercury levels and compare these data

to those generated in other geographic areas;

- laboratory research exploring dietary factors such as vitamin E and C, selenium, protein and fish oils on the pharmacokinetics of methylmercury;
- trace metal monitoring of marine mammal species with a greater emphasis on clarifying the ratio of methylmercury to total mercury for each species by tissue type, and additional characterization of organic mercury compounds and their bioavailability and toxicity;
- fish mercury monitoring studies, particularly for inland watersheds;
- provision of fish and marine mammal monitoring data in wet weight or in dry weight with the percent moisture content of fish so that data can be more readily interpreted from a risk assessment perspective;

- development of culturally appropriate communication materials to address community concerns.

Based upon the full range of information available, the Alaska Division of Public Health supports unlimited consumption of fish and marine mammals. Fish and marine mammals provide an inexpensive and readily available source of nutrients, essential fatty acids, antioxidants, calories, and protein to Alaska residents and Native peoples and may provide health benefits such as protection against NIDDM, cardiovascular disease, and improved maternal nutrition and neonatal and infant brain development. Fish and marine mammals can provide an important component to a healthy varied diet consisting of other sources of protein, such as game meats, grain products, vegetables and fruit.

Table 1: Published studies which examined total mercury (Hg) and methylmercury (MeHg) in marine mammal livers in Alaska or Canada.

Reference	Date Collected	Animal	Mean Hg (μg/g), ww	SD Hg	Hg N	Mean MeHg (μg/g),ww	SD MeHg	MeHg N
Alaska								
(Becker et al. 1995)	1989-90	Beluga Whale	28.00	27.50	11	0.788	0.688	6
(Behlke et al. 1996)	1989-95	Beluga Whale				0.974	0.623	16
(Becker et al. 1995)	1989-93	Ringed Seal	1.970	2.030	9	0.410	0.234	4
Canada								
(Smith et al. 1975)	1973	Bearded Seal	143.0	170.0	6	0.300	0.260	6
(Smith et al. 1975)	1974	Bearded Seal	26.20	26.10	56	0.120	0.400	10
(Smith et al. 1975)	1976	Ringed Seal	16.10	13.80	27	0.890	0.450	10
(Smith et al. 1975)	1976	Ringed Seal	3.760	3.420	33	0.500	0.240	8
(Smith et al. 1975)	1972-73	Ringed Seal	27.50	30.10	83	0.960	0.450	42
(Smith et al. 1975)	1977	Ringed Seal	25.50	15.00	112	0.850	0.390	13

Abbreviations used include: ww, wet weight; N, number of samples; SD, standard deviation.

Source: (Ponce et al. 1996)

Table 2: **Published studies on total mercury (Hg) tissue levels (μg/g) in marine mammals in Alaska**

Reference	Date Collected	Animal	Tissue	Mean Hg (μg/g), ww	SD Hg	Hg N
(Becker et al. 1995)	1989-90	Beluga Whale	L	28.00	27.50	11
(Becker et al. 1995)	1989-93	Ringed Seal	L	1.970	2.030	9
(Demilralp et al. 1995)	1993	Ringed Seal	L	1.330	1.930	4
(Becker et al. 1995)	1989-93	Bearded Seal	L	4.170	4.560	3
(Galster 1971)		Bearded Seal	L	1.910	1.200	4
(Galster 1971)		Bearded Seal	M	0.200	0.150	7
(Goldblatt et al. 1983)	1975	Northern Fur Seal	L	10.70	6.530	37
(Miles et al. 1992)	1976-78	Harbor Seal	L	5.000	5.000	23
(Anas 1974)	1971	Harbor Seal	L	4.230	4.250	3
(Lentfer 1976)	1972	Polar Bear	L	4.800	1.460	9
(Lentfer 1976)	1972	Polar Bear	L	3.920	1.280	16
(Lentfer 1976)	1972	Polar Bear	M	0.040	0.014	12
(Lentfer 1976)	1972	Polar Bear	M	0.040	0.260	4
(Byrne et al. 1985)	1979-80	Bowhead Whale	B	0.007	0.007	7
(Bratton et al. 1990)	1986	Bowhead Whale	B	0.003	0.005	6
(Byrne et al. 1985)	1979-80	Bowhead Whale	K	0.006	0.006	2
(Bratton et al. 1990)	1986	Bowhead Whale	K	0.005	0.001	6
(Bratton et al. 1990)	1988	Bowhead Whale	K	0.007	0.001	4
(Byrne et al. 1985)	1979-80	Bowhead Whale	L	0.005	0.005	2
(Bratton et al. 1990)	1986	Bowhead Whale	L	0.008	0.001	6
(Bratton et al. 1990)	1988	Bowhead Whale	L	0.007	0.001	4
(Becker et al. 1995)	1992-93	Bowhead Whale	L	0.170	0.110	3
(Byrne et al. 1985)	1979-80	Bowhead Whale	M	0.001	0.001	2
(Bratton et al. 1990)	1986	Bowhead Whale	M	0.003	0.001	6
(Bratton et al. 1990)	1988	Bowhead Whale	M	0.002		1
(Taylor et al. 1989)	1981-84	Pacific Alaska Walrus	L	1.500	3.180	62
(Galster 1971)		Pacific Alaska Walrus	L	0.490	0.100	7
(Galster 1971)		Pacific Alaska Walrus	M	0.020	0.005	6

Abbreviations used include: ww, wet weight; B, blubber; K, kidney; L, Liver; M, muscle; N, number of samples; SD, standard deviation.

Source: (Ponce et al. 1996)

Table 3: Published studies on total mercury (Hg) tissue levels (μg/g) in marine mammals in Canada.

Reference	Date Collected	Animal	Tissue	Mean Hg (μg/g), ww	SD Hg	Hg N
(Muir et al. 1992c)	1977	Beluga Whale	B	0.080	0.090	11
(Lutz, unpubl. in Muir, 1992)	1971	Beluga Whale	L	6.260	3.710	7
(Muir et al. 1992c)	1977	Beluga Whale	L	30.60	20.50	8
(Bligh, unpubl. in Muir, 1992)	1971	Beluga Whale	M	0.970	0.970	1
(Lutz, unpubl. in Muir, 1992)	1972	Beluga Whale	M	0.710	0.140	7
(Lutz, unpubl. in Muir, 1992)	1971	Beluga Whale	M	0.530	0.530	43
(Muir et al. 1992c)	1977	Beluga Whale	M	2.120	1.150	11
(Smith et al. 1975)	1975	Ringed Seal	L	19.30	18.40	88
(Smith et al. 1975)	1976	Ringed Seal	L	16.10	13.80	27
(Smith et al. 1975)	1976	Ringed Seal	L	0.320	0.800	36
(Smith et al. 1975)	1976	Ringed Seal	L	3.760	3.420	33
(Smith et al. 1975)	1972	Ringed Seal	L	1.000	1.160	13
(Smith et al. 1975)	1972-73	Ringed Seal	L	27.50	30.10	83
(Smith et al. 1975)	1977	Ringed Seal	L	25.50	15.00	112
(Fallis, unpubl. in Muir, 1992)	1975	Ringed Seal	L	32.70	0.750	5
(Fallis, unpubl. in Muir, 1992)	1975	Ringed Seal	K	2.320	2.320	1
(Smith et al. 1975)	1975	Ringed Seal	M	0.440	0.160	89
(Smith et al. 1975)	1976	Ringed Seal	M	0.910	0.380	27
(Smith et al. 1975)	1976	Ringed Seal	M	0.080	0.070	37
(Smith et al. 1975)	1976	Ringed Seal	M	0.310	0.170	33
(Smith et al. 1975)	1972	Ringed Seal	M	0.230	0.110	13
(Smith et al. 1975)	1972-73	Ringed Seal	M	0.720	0.330	83
(Fallis, unpubl. in Muir, 1992)	1977	Ringed Seal	M	0.330	0.060	7
(Smith et al. 1975)	1973	Bearded Seal	L	143.0	170.0	6
(Smith et al. 1975)	1974	Bearded Seal	L	26.20	26.10	56
(Smith et al. 1975)	1973	Bearded Seal	M	0.530	0.350	3
(Smith et al. 1975)	1974	Bearded Seal	M	0.090	0.040	55

Abbreviations used include: ww, wet weight; B, blubber; K, kidney; L, Liver; M, muscle; N, number of samples; SD, standard deviation

Source: (Ponce et al. 1996).

Table 4: **Allowable Routine Weekly Intake of Seafood (in pounds) by an average weight 60 kg woman of reproductive age based upon varying concentrations of Hg in seafood and agency guidelines**

	USEPA	WHO
Daily dose of MeHg (μg/kg/day)	0.1	0.47
Seafood Hg concentration (ppm)		
0.01[a]	9.3	46.5
0.05[b,c]	1.9	9.3
0.25[d]	0.4	1.9
0.60[e]	0.2	0.8
0.90[f]	0.1	0.5

a. Methylmercury in bowhead whale liver (0.01 ppm), muscle or blubber tissues (0.001 ppm) are at or below these concentration (see Tables 1-3).

b. Average total mercury in anchovy, butterfish, clams, herring, haddock, kingfish, mullet, salmon, silver hake, spotfish, squid, smelts, and trout is 0.05 ppm (Stern 1996 NMFS, in USEPA, 1995).

c. Average Methylmercury in beluga blubber tissues are 0.06 ppm (see Tables 1-3).

d. Average total mercury in bass, crappie, dolphin, halibut, lobster, mackerel, pike, and snapper range from 0.2-0.3ppm (Lowe et al. 1985; Stern 1996).

e. Average estimated beluga muscle concentrations. This level is based on Canadian and Greenland data and assumes that 80% of total Hg is MeHg (Tables 1-3).

f. Average total mercury levels for swordfish and shark (Stern 1996 NMFS, in USEPA, 1995). Also, the high-end of values of Hg identified in older/larger marine finfish approach or could exceed 1 ppm. Also, older fresh water piscivorous fish may exceed 1 ppm.

Table 5: Selenium concentrations in marine mammals in Alaska

Reference	Date Collected	Animal	Tissue	Mean Se (µg/g), ww	SD Se	Se N
(Byrne et al. 1985)	1979-80	Bowhead Whale	B	0.001	0.001	7
(Bratton et al. 1990)	1986	Bowhead Whale	B	0.005	0.005	6
(Byrne et al. 1985)	1979-80	Bowhead Whale	K	0.028	0.028	2
(Bratton et al. 1990)	1986	Bowhead Whale	K	1.590	0.330	6
(Bratton et al. 1990)	1988	Bowhead Whale	K	1.760	0.200	4
(Byrne et al. 1985)	1979-80	Bowhead Whale	L	0.080	0.080	2
(Bratton et al. 1990)	1986	Bowhead Whale	L	1.330	0.300	6
(Bratton et al. 1990)	1988	Bowhead Whale	L	1.250	0.190	4
(Becker et al. 1995)	1992-93	Bowhead Whale	L	0.914	0.396	3
(Byrne et al. 1985)	1979-80	Bowhead Whale	M	0.130	0.130	2
(Bratton et al. 1990)	1986	Bowhead Whale	M	0.420	0.160	6
(Bratton et al. 1990)	1988	Bowhead Whale	M	0.470		1
(Becker et al. 1995)	1989-90	Beluga Whale	L	19.50	18.00	15
(Becker et al. 1995)	1989-93	Bearded Seal	L	3.070	2.040	3
(Miles et al. 1992)	1976-78	Harbor Seal	L	1.600	1.600	23
(Taylor et al. 1989)	1981-84	Pacific Walrus	K	9.530	6.320	3
(Taylor et al. 1989)	1981-84	Pacific Walrus	L	2.320	1.960	65
(Becker et al. 1995)	1989-93	Ringed Seal	K	3.150	3.150	2
(Becker et al. 1995)	1989-93	Ringed Seal	L	2.960	1.460	14

Abbreviations used include: ww, wet weight; B, blubber; K, kidney; L, Liver; M, muscle; N, number of samples; SD, standard deviation
Source: (Ponce et al. 1996).

Table 6: Studies of Human Hair Mercury Concentrations in Alaska

Author/Agency and Year	Location	Hair Hg (µg/g) Mean	(SD or Range)	N
(CDC 1972)	Pribilof Islands			
	Liver	5.6	(1.7)	15
	No Seal Liver	4.9	(2.2)	13
	Total Alaska Native	4.6	(1.0)	28
	Whites	3.4	(2.2)	6
(AKDHSS 1972)	Pribilof Islands	5.8	(0.3 - 13.2)	13
	Bethel Mothers	5.1	(1.5 - 9.1)	14
	Juneau	1.5	(0.7 - 2.4)	8
	Y-K River Villages	1.2	(0.0 - 3.0)	56
(Galster 1976)	Y-K Coastal	4.3	(0.6)	12
	Y-K Interior	3.6	(0.7)	6
	Urban	4.0	(0.8)	4
(Crecelius et al. 1990)	Nome Women	1.0	(1.0)	200
(Lasorsa et al. 1991)	Nome Women	1.4	(1.0)	80

Figure 1:   Lowest Observed Adverse Effect Level (LOAEL) of Methylmercury in Adults Based Upon Paresthesia in Japan.
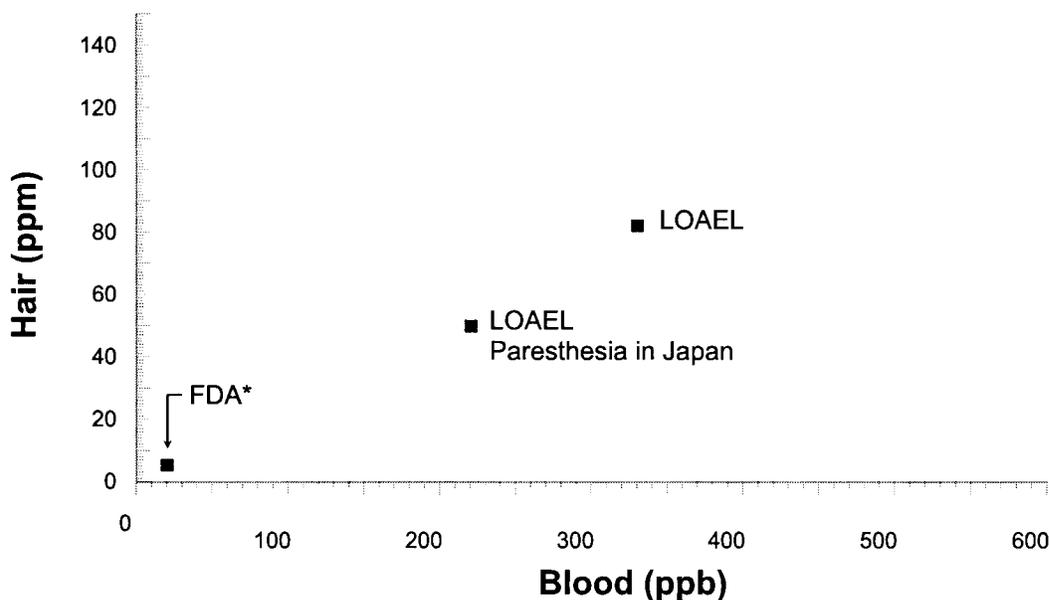
* The LOAEL was paresthesia in an adult at hair mercury concentrations of 52 ppm. Current FDA and WHO guidelines incorporate a margin of safety with hair concentrations of 5-6 ppm and blood concentrations of 20 ppb being recommended as allowable exposures. These values correspond to the WHO Provisional Tolerable Weekly Intake for the average weight, 70-kg, adult which is 230 μg for MeHg or 300 μg for total Hg, or a calculated dietary intake of 0.47 μg/kg/day. Source: (Tollefson et al. 1986; WHO 1990).

Hair of the individual with paresthesia at the lowest hair concentration observed (52 ppm) was reanalyzed using the atomic absorption analytic technique. The reanalyses provided a higher hair concentration (86 ppm) than what was previously measured. Source: (WHO 1990).

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Figure 2: The percent of abnormal findings for limb tone, deep tissue reflex, and overall neurological exam by maternal hair mercury concentrations, Seychelles Child Development Study.
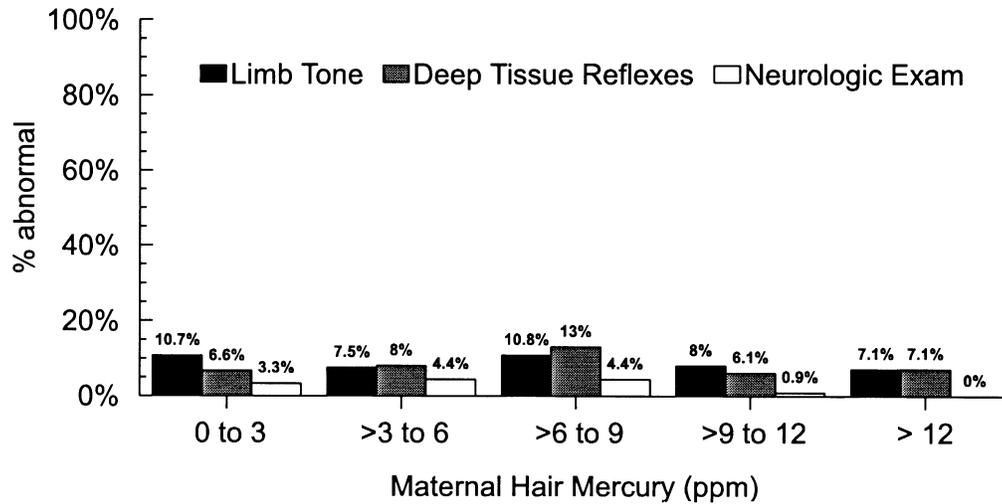
Source: (Myers et al. 1995 Summary).

Figure 3: Percent of children with questionable scores on the Revised Denver Developmental Screening Test, by category of maternal hair mercury concentrations (ppm), Seychelles Child Development Study.
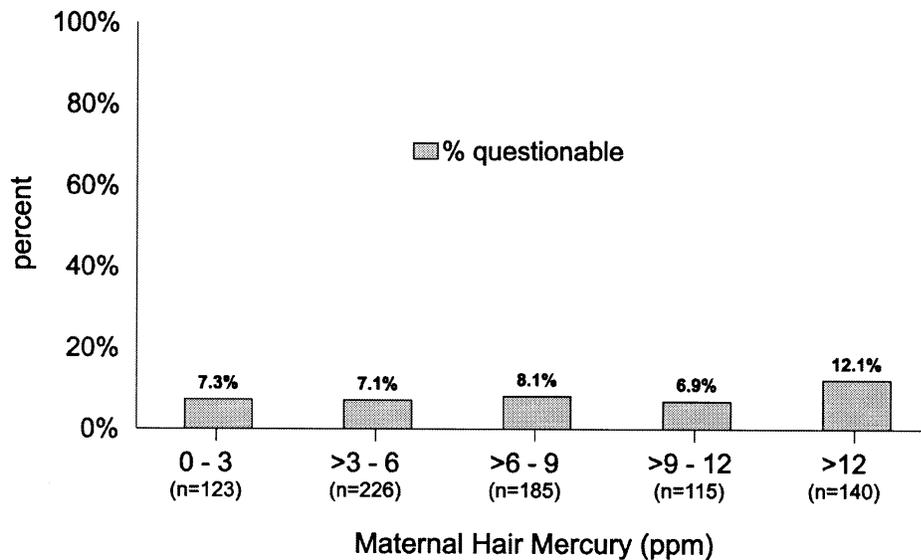
Source: (Myers et al. 1995 Summary)

Note: Only 3 individuals had abnormal test scores: one in the 3-6 ppm, one in the 6-9 ppm, and one in the > 12 ppm maternal hair exposure categories.

References

AKDHSS (1972). Pilot Evaluation, Human Risk from Mercury in Alaska: Alaska Department of Health and Social Services, Division of Public Health, Community Health Section: unpublished.

Alexander, J., T. Norseth (1979). "The effect of selenium on the biliary excretion and organ distribution of mercury in the rat after exposure to methyl mercuric chloride." Acta Pharmacol Toxicol 44(3):168-76.

Al-Shahristani, H., K. Shihab, I.K. Al-Haddad (1976). "Mercury in hair as an indicator of total body burden." Bull World Health Organ 53:105-112.

Amin-Zaki, L., S. Elhassani, M.A. Majeed, T.W. Clarkson, R.A. Doherty, M. Greenwood (1974). "Intra-uterine methylmercury poisoning in Iraq." Pediatrics 54(5):587-95.

Anas, R.E. (1974). "Heavy Metals in the Northern Fur Seal, *Callorhinus ursinus*, and Harbor Seal, *Phoca vitulina richardi*." Fishery Bulletin 62(1):133-137.

ATSDR (1994). Toxicological Profile for Mercury: US Department of Health and Human Services: Agency.

Bakir, F., S.F. Damluji, L. Amin-Zaki, M. Murtadha, A. Khalidi, N.Y. al-Rawi, S. Tikriti, H.I. Dahahir, T.W. Clarkson, J.C. Smith, R.A. Doherty (1973). "Methylmercury poisoning in Iraq." Science 181(96):230-41.

Bauernfeind, J. (1980). "Tocopherols in Foods". Vitamin E, A Comprehensive Treatise Marcel Dekker Inc:99-168.

Becker, P.R., E.A. Mackey, M. M. Schantz, R.R. Greenberg, B.J. Koster, S.A. Wise, D.C.G. Muir (1995). Concentrations of Chlorinated Hydrocarbons, Heavy Metals and Other Elements in Tissues Banked by the Alaska Marine Mammal Tissue Archival Project: U.S. DOC, National Institute of Standards and Technology NISTIR 5620.

Behlke, M.K., M. Schantz (1996). Determination of methylmercury in beluga whale livers by gas chromatography - atomic emission detection: U.S. Department of Commerce, National Institute of Standards and Technology: NIST Report of Analysis 839.02-96-003.

Beijer, K., A. Jernelov (1978). "Ecological aspects of mercury--selenium interactions in the marine environment." Environ Health Perspect 25:43-5.

Bloom, N.S. (1992). "On the methylmercury content of fish and marine invertebrates." Can J Fish Aquat Sci 49:1010.

Born, E.W., I. Kraul, T. Kristensen (1981). "Mercury, DDT and PCB in the Atlantic Walrus (*Odobenus rosmarus rosmarus*) from the Thule District, North Greenland." Arctic 34(3):255-260.

Bornhausen, M., H.R. Musch, H. Greim (1980). "Operant behavior performance changes in rats after prenatal methylmercury exposure." Toxicol Appl Pharmacol 56:305-310.

Bratton, G.R., W. Flory, B. Spainhour (1990). Environmental Pollutant Levels in Selected Tissues from Subsistence Harvested Bowhead Whales. Fifth Conference on the Biologyu of the Bowhead Whale (*Balaena mysticetus*), Anchorage, Alaska.

Buelke-Sam, J., C.A. Kimmel, J. Adams, C.J. Nelson, C.V. Vorhess, D.C. Wright, O.V. St, B.A. Korol, R.E. Butcher, M.A. Geyer (1985). "Collaborative behavioral teratology study: results." Neurobehav Toxicol Teratol 7:591-624.

Burbacher, T.M., K.S. Grant, N.K. Mottet (1986). "Retarded object permanence development in methylmercury exposed Macaca fascicularis infants." Developmental Psychology 22(6):771-776.

Burbacher, T.M., G.P. Sackett, N.K. Mottet (1990). "Methylmercury effects on the social behavior of Macaca fascicularis infants." Neurotoxicol Teratol 12(1):65-71.

Byrne, C., R. Balasubramanian, E.B. Overton, T. F. Albert (1985). "Concentrations of Trace Metals in the Bowhead Whale." Mar Pollut Bull 16 (12):497-498.

Cappon, C.J., J.C. Smith (1981). "Mercury and selenium content and chemical form in fish muscle." Arch Environ Contam Toxicol 10(3):305-319.

Cappon, C.J., J.C. Smith (1982). "Chemical form and distribution of mercury and selenium in edible seafood." J Anal Toxicol 6(1):10-21.

CDC (1972). Possible Mercury Exposure, Pribilof Islands, Alaska: Public Health Service: unpublished EPI-71-43-2.

Cernichiari, E., T.Y. Toribara, L. Liang, D.O. Marsh, M. W. Berlin, G.J. Myers, C. Cox, C.F. Shamlaye, O. Choisy, P. Davidson, T.W. Clarkson (1995). "The biological monitoring of mercury in the Seychelles study." NeuroToxicology 16(4):613-628.

Chan, H.M., C. Kim, K. Khoday, O. Receveur, H.V. Kuhnlein (1995). "Assessment of dietary exposure to trace metals in Baffin Inuit food." Environ Health Perspect 103:740-746.

Chang, L.W., M. Gilbert, J. Sprecher (1978). "Modification of methylmercury neurotoxicity by vitamin E." Environmental Research 17(3):356-366.

Chang, L. W., R. Suber (1982). "Protective effect of selenium on methylmercury toxicity: a possible mechanism." Bull Env Contam Tox 29(3):285-9.

Chen, R.W., V.L. Lacy, P.D. Whanger (1975). "Effect of selenium on methylmercury binding to subcellular and soluble proteins in rat tissues." Res Commun Chem Pathol Pharmacol 12(2):297-308.

Chou, C.L., J.F. Uthe (1978). Heavy Metal Relationships in Lobster (Homarus americanus) and Rock Crab (Cancer irroratus) Digestive Glands: International Council for the Exploration of the Sea: Rep. E:15/C.M.

Clarkson, T. (1991). "Methylmercury." Fundam Appl Toxicol 16(1):20-1.

Clarkson, T.W. (1977). "Mercury Poisoning". Clinical Chemistry and Chemical Toxicology of Metals, Amsterdam Elsevier. 1:189-200.

Cox, C., T.W. Clarkson, D.O. Marsh, L. Amin-Zaki, S. a. Tikriti, G.G. Myers (1989). "Dose-response analysis of infants prenatally exposed to methyl mercury: an application of a single compartment model to single-strand hair analysis." Environmental Research 49(2):318-332.

Crecelius, E.A., C.W. Apts, B. K. Lasorsa (1990). Concentrations of Metals in Norton Sound Seawater Samples and Human Hair Samples, 1990: U.S. Department of the Interior Minerals Management Service Alaska OCS Region, Battelle/Marine Sciences Laboratory: OCS Study MMS 90-0010.

Crump, K., J. Viren, A. Silvers, H.I. Clewell, J. Gearhart, A. Shipp (1995). "Reanalysis of dose-response data from the Iraqi methylmercury poisoning episode." Risk Analysis 15(4):523-532.

Davidson, P.W., G.J. Myers, C. Cox, C. Shamlaye, O. Choisy, J. Sloane-Reeves, E. Cernichiari, D.O. Marsh, M. Berlin, M. Tanner, T. W. Clarkson (1995). "Neurodevelopmental test selection, administration, and performance in the main Seychelles child development study." NeuroToxicology 16(4):665-676.

Demilralp, R., E.A. Mackey, B.J. Koster (1995). Analysis of liver tissues from pilot whale, white-sided dolphins, ringed seals, and bearded seals: U.S. Department of Commerce, National Institute of Technology: NIST Report of Analysis 839.08-95-008.

Eaton, R.D., D.C. Secord, P. Hewitt (1980). "An experimental assessment of the toxic potential of mercury in ringed seal liver for adult laboratory cats." Toxicol Appl Pharmacol 55(3):514-521.

Egeland GM, J.P. Middaugh (1997). Fish consumption: Balancing benefits with mercury risks. Science 278:1904-1905.

Eide, R., R.O. Peterson (1997). "Changes in mercury exposure in the Great Lakes area, USA, as shown by the mercury content of moose molars." International Conference on Human Health Effects of Mercury Exposure, Torshavn, Faroe Islands, June 22-26. Poster No. 30, page 86 of abstract book.

FDA, A.M. Adams (1993). "Methyl mercury in salmon", correspondence.

Freeman, H.C., G. Shum, J.F. Uthe (1978). "The selenium content in swordfish (Xiphias gladius) in relation to total mercury content." J Environ Sci Health 13(A):235.

Galster, W.A. (1976). "Mercury in Alaskan Eskimo mothers and infants." Environ Health Perspect 15: 135-140.

Galster, W.R. (1971). Accumulation of mercury in Alaskan pinnepeds. Twenty-second Alaska Science Conference, College, Alaska.

Ganser, A.L., D.A. Kirschner (1985). "The interaction of mercurials with myelin: comparison of in vitro and in vivo effects." NeuroToxicology 6 (1):63-78.

Ganther, H.E. (1980). "Interactions of vitamin E and selenium with mercury and silver." Ann N Y Acad Sci 355:212-26.

Ganther, H.E., C. Goudie, M.L. Sunde, M.J. Kopecky, P. Wagner (1972). "Selenium: Relation to decreased toxicity of methylmercury added to diets containing tuna." Science 175(26):1122-1124.

Geyer, M.A., R.E. Butcher, K. Fite (1985). "A study of startle and locomotor activity in rats exposed prenatally to methylmercury." Neurobehav Toxicol Teratol 7:759-765.

Gilbert, S.G., T.M. Burbacher, D.C. Rice (1993). "Effects of in utero methylmercury exposure on a spatial delayed alternation task in monkeys." Toxicol Appl Pharmacol 123(1):130-136.

Gilbert, S.G., K.S. Grant-Webster (1995). "Neurobehavioral effects of developmental methylmercury exposure." Environ Health Perspect 103(6):135-142.

Gilbert, S.G., D.C. Rice, T. M. Burbacher (1996). "Fixed interval/fixed ratio performance in adult monkeys exposed in utero to methylmercury." Neurotoxicol Teratol 18(5):539-546.

Gilmour, C.C., E.A. Henry (1991). "Mercury methylation in aquatic systems affected by acid deposition." Environ Pollut 71(2-4):131-169.

Goldblatt, C.J., R.G. Anthony (1983). "Heavy Metals in Northern Fur Seals (*Callorhinus ursinus*) from the Pribilof Islands, Alaska." J Environ. Qual 12(4):478-482.

Grandjean, P., P. Weihe, P J. Jorgensen, T. Clarkson, E. Cernichiari, T. Videro (1992). "Impact of maternal seafood diet on fetal exposure to mercury, selenium, and lead." Archives of Environmental Health 47(3):185-195.

Grandjean, P., P. Weihe, J.B. Nielsen (1994). "Methylmercury: significance of intrauterine and postnatal exposures." Clin Chem 40 (7 Pt 2):1395-1400.

Grandjean, P., P. Weihe, R.F. White (1995). "Milestone development in infants exposed to methylmercury from human milk." NeuroToxicology 16(1):27-34.

Grandjean, P., P. Weihe, R.F. White, F. Debes, S. Araki, K. Yokoyama, K. Murata, N. Sorensen, R. Dahl, P. J. Jorgensen (1997). "Cognitive deficit in 7-year old children with prenatal exposure to methylmercury." Neurotoxicol Teratol 19:417-428.

Grieg, R.A., J. Jones (1976). "Nondestructive neutron activation analysis of marine organisms collected from ocean dump sites of the middle eastern United States." Arch Environ Contam Toxicol 4:420.

Groth, D.H., H. Stettler, G. MacKay (1976). "Interactions of mercury, cadmium, selenium, tellurium, arsenic, and beryllium". Effects and Dose-Response Relationships of Toxic Metals, Amsterdam Elsevier Scientific Publishing Co.:527.

Guinn, V.P., R. Kishore (1974). "Results from multi-trace-element neutron activation analyses of marine biological specimens." J Radioanal Chem 19:367.

Gunderson, V.M., K.S. Grant, T.M. Burbacher, J.F. Fagan, N.K. Mottet (1986). "The effect of low-level prenatal methylmercury exposure on visual recognition memory in infant crab-eating macaques." Child Development 57:1076-1083.

Gunderson, V.M., K.S. Grant-Webster, T.M. Burbacher, N.K. Mottet (1988). "Visual recognition memory deficits in methylmercury-exposed Macaca fascicularis infants." Neurotoxicol Teratol 10(4):373-379.

Hall, R.A., E.G. Zook, G.M. Meaburn (1978). National Marine Fisheries Service Survey of trace elements in the fishery resource: National Oceanic and Atmospheric Administration: NOAA Technical Report NMFS SSRF-721:1-6.

Hansen, J.C. (1988). "Has selenium a benfeicial role in human exposure to inorganic mercury?" Med Hypotheses 25(1):45-53.

Hansen, J.C. (1990). "Human exposure to metals through consumption of marine foods: A case study of exceptionally high intake among Greenlanders". Heavy Metals in the Marine Environment, Boca Raton, FL CRC Press, Inc.:227-243.

Hansen, J.C., T.Y. Toribara, A.G. Muhs (1989). "Trace metals in human and animal hair from the 15th century graves at Qilakitsoq compared with recent samples." Meddelelser om Gronland 12:161-167.

Headlee, P.G. (1996). Mercury and Selenium Concentrations in Fish Tissue and Surface Waters of the Northern Unnit of the Innoko National Wildlife Refuge (Kaiyuh Flats), West Central Alaska, 1993: Tanana Chiefs Conference Inc. Wildlife and Parks Program: Water Resources 96-3.

Hirota, Y., S. Yamaguchi, N. Shimojo, K. Sano, K. Tadokoro (1980). "[Effects of various mercury compounds on the activity of glutathione peroxidase (author's transl)]." Sangyo Igaku 22(5):388-9.

Hirota, Y., S. Yamaguchi, N. Shimojoh, K. I. Sano (1980). "Inhibitory effect of methylmercury on the activity of glutathione peroxidase." Toxicol Appl Pharmacol 53(1):174-6.

Hochberg, F.H., S.A. Sherman, M.B. Gregg (1972). Possible mercury exposure, Pribilof Islands, Alaska: Viral Diseases Branch, Epidemiology Program, CDC PHS, EPI-71-43-2.

Hojbjerg, S., J.B. Nielsen, O. Anderson (1997). Dietary factors decrease the whole-body retention in mice orally exposed to methylmercury. International Conference on Human Health Effects of Mercury Exposure, Torshavn, Faroe Islands. Poster No 65:121.

Ihnat, M., J. Aaseth, M.L. Berrow, S.S. Berman, GA. Cutter, R.A. Duce, R.C. Ewan, S.A. Lewis, J.O. Nriagu, B.W. Mosher, A. Schubert, D.L. Rabenstein, K.S. Tan, K.W.M. Siu, Y. Thommassen, A.M. Ure, C. Veillon, W.R. Wolf (1989). Occurrence and Distribution of Selenium. Boca Raton, Florida, CRC Press Inc 354.

Inouye, M., K. Murao, Y. Kajiwara (1985). "Behavioral and neuropathological effects of prenatal methylmercury exposure in mice." Neurobehav Toxicol Teratol 7:227-232.

IRIS, I.R.I.S. (1992). U Methylmercury. Washington, U.S. Environmental Protection Agency.

Johansen, P. (1981). Heavy metals in marine mammals and heavy metal intake in humans in Greenland: Nordic Council for Arctic Medical Research Series 33.

Kari, T., P. Kauranen (1978). "Mercury and selenium contents of seals from fresh and brackish waters in Finland." Bull Env Contam Tox 19 (3):273-80.

Kasuya, M. (1975). "The effect of vitamin E on the toxicity of alkyl-mercurials on nervous tissue in culture." Toxicol Appl Pharmacol 32:347-354.

Kinjo, Y., Y. Takizawa, Y. Shibata, M. Watanabe, H. Kato (1995). "Threshold dose for adults exposed to methylmercury in Niigata Minamata Disease Outbreak." Environmental Sciences 3:91-101.

Kjellstrom, T., P. Kennedy, S. Wallis, A. Stewart, L. Friberg, B. Line, T. Wutherspoon, C. Mantell (1989). Physical and Mental Development of Children with Prenatal Exposure to Mercury from Fish: National Swedish Environmental Protection Board 3642.

Koeman, J.H., W.S. van de Ven, J.J. de Goeij, P.S. Tjioe, J.L. van Haaften (1975). "Mercury and selenium in marine mammals and birds." Science of the Total Environment 3(3):279-87.

Kutsuna, M. (1968). Minamata Disease: Study Group of Minamata Disease. Kumamoto University, Japan.

Lasorsa, B.K., R.J. Citterman (1991). Segmental analysis of mercury in hair in 80 women of Nome, Alaska: Batelle/Marine Sciences Laboratory OCS Study MMS 91-0065.

Lentfer, J.W. (1976). Environmental Contaminants and Parasites in Polar Bears: Alaska Department of Fish and Game: Final W-17-4 and W-17-5, Job 5.5R.

Lowe, T.P., T.W. May, W.G. Brumbaugh, D.A. Kane (1985). "National Contaminant Biomonitoring Program: concentrations of seven elements in freshwater fish 1978-1981." Arch Environm Contam Toxicol 14:363-388.

Luten, J.B., A. Ruiter, T.M. Ritskes, A.B. Rauchbaar (1980). "Mercury and selenium in marine and freshwater fish." J Food Sci 45:416.

MacKay, N.J., M.N. Kazacos, R.J. Williams, M.I. Leedow (1975). "Selenium and heavy metals in black marlin." Mar Pollut Bull 6:57.

Magos, L., T.W. Clarkson, A.R. Hudson (1984). "Differences in the effects of selenite and biological selenium on the chemical form and distribution of mercury after the simultaneous administration of HgCl2 and selenium to rats." J Pharmacol Exp Ther 228(2):478-83.

Magos, L., T.W. Clarkson, S. Sparrow (1987). "Comparison of the protection given by selenite, selenomethionine and biological selenium against the renotoxicity of mercury." Arch Toxicol 60:422-426.

Magos, L., M. Webb (1977). "The effect of selenium on the brain uptake of methylmercury." Arch Toxicol 38(3):201-7.

Marsh, D.O., T.W. Clarkson, C. Cox, G.J. Myers, L. Amin-Zaki, S. Al-Tikriti (1987). "Fetal methylmercury poisoning: Relationship between concentration in single strands of maternal hair and child effects." Arch Neurol 44:1017-1022.

Marsh, D.O., G.J. Myers, T.W. Clarkson, L. Amin-Zaki, S. Tikriti, M.A. Majeed (1980). "Fetal methylmercury poisoning: clinical and toxicological data on 29 cases." Ann Neurol 7(4):348-53.

Marsh, D.O., G.J. Myers, T.W. Clarkson, L. Amin-Zaki, S. Tikriti, M.A. Majeed, A.R. Dabbagh (1981). "Dose-response relationship for human fetal exposure to methylmercury." Clin Toxicol 18 (11):1311-8.

Marsh, D.O., M.D. Turner, J.C. Smith, P. Allen, N. Richdale (1995). "Fetal methylmercury study in a Peruvian fish-eating population." NeuroToxicology 16(4):717-726.

McKeown-Eyssen, G.E., J. Ruedy, A. Neims (1983). "Methyl mercury exposure in northern Quebec. II. Neurologic findings in children." Am J Epidemiol 118(4):470-479.

Miettinen, J.K. (1973). "Absorption and elimination of dietary mercury (2+) ion and methylmercury in man". Mercury, Mercurials, and Mercaptans: Proceedings 4th International Conference on Environmental Toxicology, Rochester Plenum Press: 233-243.

Miles, A.K., D.G. Calkins, N.C. Coon (1992). "Toxic Elements and Organochlorines in Harbor Seals (*Phoca vitulina richardsi*), Kodiak, Alaska, USA." Bull Environ Contam Toxicol 48:727-732.

Miller, C.T., D. Krewski, L. Tryphonas (1985). "Methylmercury-induced mitochondrial DNA synthesis in neural tissue of cats." Fundam Appl Toxicol 5:251-264.

Muir, D.C., R. Wagemann, B.T. Hargrave, D.J. Thomas, D.B. Peakall, R.J. Norstrom (1992c). "Arctic marine ecosystem contamination." Science of the Total Environment 122(1-2):75-134.

Myers, G.J., P.W. Davidson, C. Cox, C.F. Shamlaye, M.A. Tanner, D.O. Marsh, E. Cernichiari, L.W. Lapham, M. Berlin, T.W. Clarkson (1995). "Summary of the Seychelles child development study of the relationship of fetal methylmercury exposure to neurodevelopment." NeuroToxicology 16(4):711-716.

Myers, G.J., D.O. Marsh, C. Cox, P.W. Davidson, C.F. Shamlaye, M.A. Tanner, A. Choi, E. Cernichiari, O. Choisy, T.W. Clarkson (1995). "A pilot neurodevelopmental study of Seychellois children following in utero exposure to methylmercury from a maternal fish diet." NeuroToxicology 16(4):629-638.

Naganuma, A., N. Imura (1981). "Properties of mercury and selenium in a high molecular weight substance in rabbit tissues formed by simultaneous administration." Pharmacol Biochem Behav 15:449-454.

Nobmann, E.D., T. Byers, A.P. Lanier, J.H. Hankin, M.Y. Jackson (1992). "The diet of Alaska Native adults: 1987-1988." Am J Clin Nutr 55:1024-1032.

Ohi, G., S. Nishigaki, H. Seki, Y. Tamura, T. Maki, H. Maeda, S. Ochiai, H. Yamada, Y. Shimamura, H. Yagyu (1975). "Interaction of dietary methylmercury and selenium on accumulation and retention of these substances in rat organs." Toxicol Appl Pharmacol 32:527-533.

Ohi, G., S. Nishigaki, H. Seki, Y. Tamura, T. Maki, K. Minowa, Y. Shimamura, I. Mizoguchi, Y. Inaba, Y. Takizawa, Y. Kawanishi (1980). "The protective potency of marine animal meat against the neurotoxicity of methylmercury: its relationship with the organ distribution of mercury and selenium in the rat." Food Cosmet Toxicol 18(2):139-45.

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Ponce, R.A., G.M. Egeland, J.P. Middaugh, P.R. Becker (1996). Twenty Years of Trace Metal Analyses of Marine Mammals: Evaluation and Summation of Data from Alaska and Other Arctic Regions. ProceedingsTenth International Conference on Circumpolar Health, in press.

Potter, S.Q., G. Matrone (1973). "Effect of selenite on the toxicity and retention of dietary methyl-mercury and mecuric chloride." Fed Proc 32:929.

Rice, D.C. (1989). "Delayed neurotoxicity in monkeys exposed developmentally to methyl-mercury." NeuroToxicology 10:645-650.

Rice, D.C. (1992). "Effects of pre- plus postnatal exposure to methylmercury in the monkey on fixed interval and discrimination reversal performance." NeuroToxicology 13:443-452.

Rice, D.C., S.G. Gilbert (1982). "Early chronic low-level methylmercury poisoning in monkeys impairs spatial vision." Science 216(4547):759-761.

Rice, H.E., N.S. Adzick (1993). "Prenatal diagnosis: essentials for the pediatric surgeon." Semin Pediatr Surg 2(2):84-91.

Rowland, I.R., P. Grasso, M.J. Davies (1975). "The methylation of mercuric chloride by human intestinal bacteria." Experientia 31(9):1064-1065.

Rusanowski, P.C., L.E. Gardner, S.C. Jewett (1987). Nome Offshore Placer Project: Inspiration Gold, Inc., Nome, Alaska/NORTEC, a Division of ERT: Annual Report 1986.

Sager, P.R., R.A. Doherty, P.M. Rodier (1982). "Morphometric analysis of the effect of methyl mercury on developing mouse cerebellar cortex." Toxicologist 2:116.

Satoh, H., N. Yasuda, S. Shimai (1985). "Development of reflexes in neonatal mice prenatally exposed to methylmercury and selenite." Toxicol Lett 25(2):199-203.

Shamlaye, C.F., D.O. Marsh, G.J. Myers, C. Cox, P.W. Davidson, O. Choisy, E. Cernichiari, A. Choi, M.A. Tanner, T.W. Clarkson (1995). "The Seychelles child development study on neuro-developmental outcomes in children following in utero exposure to methylmercury from a maternal fish diet: background and demographics." NeuroToxicology 16(4):597-612.

Shkilnyk, A.M. (1985). A Poison Stronger than Love: The Destruction of an Ojibwa Community. New Haven, Yale University Press 275.

Shultz, C.D., B.M. Ito (1979). "Mercury and selenium in blue marlin, *Makaira nigricans,* from the Hawaiian Islands." Fish Bull 76:872.

Skerfving, S. (1974). "Methylmercury exposure, mercury levels in blood and hair, and health status in Swedes consuming contaminated fish." Toxicology 2(1):3-23.

Skerfving, S.B., J.F. Copplestone (1976). "Poisoning caused by the consumption of organomercury-dressed seed in Iraq." Bull World Health Organ 54:101-112.

Smith, T.G., A.J. Armstrong (1975). "Mercury in Seals, Terrestrial Carnivores, and Principle Food Items of the Inuit, from Holman, N.W.T., Interim Report." J Fish Res Board Can 32(6):795-801.

Stern (1996). Estimation of Human Methylmercury Exposure to the General United States Population and Identified Subpopulations Through the Consumption of Fish: EPA, Science Advisory Board: Mercury Study Report to Congress, Draft Appendix H Vol III.

Stern, A.H. (1993). "Re-evaluation of the reference dose for methylmercury and assessment of current exposure levels." Risk Anal 13(3):355-364.

Stillings, B., H. Lagally, J. Soares, D. Miller (1972). Effect of cystine and selenium on the toxicological effects of methylmercury in rats. 9th Int. Congr. Tutr., Mexico City: 206.

Stillings, B.R., H. Lagally, P. Bauersfeld, J. Soars (1974). "Effect of cystine, selenium, and fish protein on the toxicity and metabolism of methylmercury in rats." Toxicol Appl Pharmacol 30:243-254.

Stokinger, H. (1981). Patty's Industrial Hygiene and Toxicology. New York, John Wiley & Sons IIA 1769-1792.

Stopford, W., L.J. Goldwater (1975). "Methylmercury in the environment: a review of current understanding." Environ Health Perspect 12:115-8.

Syversen, T.L.M. (1982). "Changes in protein and RNA synthesis in rat brain neurons after a single dose of methylmercury." Toxicology Letters 10:31-34.

Tamari, Y., K. Hiraki, Y. Nishikawa (1979). "Fluorometric determination of selenium in sediments with 2,3-diaminonaphthalene." Bunseki Kagaku 28:164.

Taylor, D.L., S. Schliebe, H. Metsker (1989). "Contaminants in blubber, liver, and kidney tissue of Pacific walruses." Mar Pollut Bull 20(9):465-468.

Tollefson, L., F. Cordle (1986). "Methylmercury in fish: a review of residue levels, fish consumption and regulatory action in the United States." Environ Health Perspect 68:203-208.

Toribara, T.Y., A.G. Muhs (1984). "Hair: A keeper of history." Arctic Anthropol 21(1):99-108.

U.S. Dept. of the Interior (1989). "1987 and 1988 contaminant results - Koyukuk, Nowitna and Northern Unit Innoko refuges": USFWS Koyukuk/Nowitna National Wildlife Refuge, written communication.

USEPA (1995). Guidance For Assessing Chemical Contaminant Data For Use In Fish Advisories Volume 1: Sampling and Analysis, Second Edition: United States Environmental Protection Agency Office of Water (4305) EPA 823-R-95-007.

USEPA (1996). Mercury Study Report to Congress Characterization of Human Health and Wildlife Risks from Anthropogenic Mercury Emmissions in the United States SAB Review Draft: Office of Air Quality Planning & Standards and Office of Research and Development EPA-452/R-96-001f Volume VI.

Vogel, D.G., R.L. Margolis, N.K. Mottet (1985). "The effects of methyl mercury binding to microtubules." Toxicol Appl Pharmacol 80:473-486.

Weihe, P., P. Grandjean, F. Debes, R. White (1996). "Health implications for Faroe Islanders of heavy metals and PCBs from pilot whales." Science of the Total Environment 186:141-148.

Welsh, S.O., J.H. Soares (1976). "The protective effect of vitamin E and selenium against methyl mercury toxicity in the Japanese quail." Nutrition Reports International 13(1):43-51.

Wheatley, B., M.A. Wheatley (1988). "Methylmercury in the Canadian Arctic environment past and present--natural or industrial?" Arct Med Res 1:163-167.

WHO (1990). Environmental Health Criteria 101: Methylmercury. Geneva, Switzerland, World Health Organization 144.

Wrench, J.J., N.C. Campbell (1981). "Protein bound selenium in some marine organisms." Chemosphere 10:1155.

Yamini, B., S.D. Sleight (1984). "Effects of ascorbic acid deficiency on methyl mercury dicyandiamide toxicosis in guinea pigs." J Environ Pathol Toxicol Oncol 5(4-5):139-150.

Yannai, S., I. Berdicevsky, L. Duek (1991). "Transformations of inorganic mercury by Candida albicans and Saccharomyces cerevisiae." Appl Environ Microbiol 57(1):245-7.

Yoshino, Y., T. Mazai, K. Nakao (1966). "Biochemical changes in the brain in rats poisoned with an alkylmercury compound, with special reference to the inhibition of protein synthesis in brain cortex slices." Journal of Neurochemistry 13:1223-1230.

Risks in Perspective - Cadmium

Executive Summary

Cadmium is a naturally occurring element in the earth's crust and is distributed in low-levels throughout the environment. Human industrial activities can be significant point sources of cadmium. To a certain extent, cadmium can be distributed considerable distances from point sources. Cadmium in soils can be taken up by plants, and animals that graze on these plants may accumulate cadmium in their tissues, particularly in the kidneys and to a lesser extent in the liver. Similarly, in oceans, cadmium from natural and anthropogenic sources enters the food chain, accumulates in tissues over time, and biomagnifies in the food chain.

Cadmium concentrations in kidney and liver of some mammals commonly consumed in Alaska are higher than in most other commonly consumed foods, generating concerns regarding the safety of liver and kidney for human consumption. The Alaska Division of Public Health extensively reviewed the published literature regarding cadmium tissue concentrations in marine and terrestrial mammals and shellfish species in Alaska. We also reviewed toxicologic and epidemiologic information regarding the health implications of cadmium exposure through the ingestion of shellfish and liver and kidney of marine and terrestrial mammals.

Monitoring data suggest that the World Health Organization's (WHO) Provisional Tolerable Weekly Intake (PTWI) of 400-500 μg of cadmium may be exceeded among a proportion of subsistence populations in the Arctic who routinely consume kidney or

liver of certain marine mammals. However, it is important to note that WHO guidelines incorporate a margin of safety and assume that the amount consumed is consumed every week of the year, every year, over a lifetime.

The WHO PTWI was developed using information from high-dose occupational and laboratory animal studies, and, in particular, an acute poisoning episode in Japan where rice contaminated by cadmium from industrial pollution was eaten. The application of the WHO PTWI to traditional foods in the Arctic may result in overly restrictive food consumption advisories that may not be warranted based upon the full range of scientific information now available.

Cadmium in the traditional diet is present in food sources high in protein and an array of elements (such as selenium, zinc, and iron), which are known to reduce the absorption and/or toxicity of cadmium. Other nutritional factors, such as the consumption of fiber and calcium also reduce cadmium absorption, illustrating the complexities in estimating dietary cadmium exposure from tissue cadmium concen-trations. These considerations may help explain why the blood cadmium levels found in Greenland, where the consumption of marine mammal organs provided estimated exposures to cadmium 10 times greater than the WHO PTWI, were similar to blood cadmium levels observed in Denmark. Similarly, in Sweden and New Zealand the consumption of shellfish provided an estimated exposure

to cadmium twice that of the WHO PTWI, but blood cadmium levels did not reflect predicted exposure.

In addition to the above considerations, cadmium in liver and kidney is largely bound to a low molecular weight protein, metallothionein (Cd-MT) or a metallothionein-like protein; considerable uncertainty remains regarding the fate and effects of ingested Cd-MT. In animal studies, protein bound cadmium in food has been noted to be preferentially distributed to the kidney where, within renal tubular cells, protein-bound cadmium would be "freed" and able to react to sensitive cell sites. Free cadmium would, in turn, induce the synthesis of MT which may be instrumental in building the kidney's resistance to cadmium exposure. In animal studies, the toxic effects (tubular dysfunction) of high doses of Cd-MT were prevented by the administration of small non-toxic doses of cadmium. Thus, extrapolating risks from high-dose acute chemical poisoning episodes may exaggerate the risks associated with chronic low-dose dietary exposures.

Recommendations and Future Directions

Based upon the full range of information available and summarized in this report, the Division of Public Health supports the unrestricted consumption of liver and kidney of arctic wildlife traditionally harvested as part of a varied and well-balanced diet. Liver and kidney are foods rich in vitamins, protein, essential elements, and calories. Cadmium absorption can be reduced by eating a well-balanced diet rich in fiber, protein, iron, and calcium. For those wishing to further reduce their dietary exposures to cadmium, limiting the consumption of liver and kidney from older marine mammals, or more often choosing a

liver meal over a kidney meal would be effective ways to do so without losing the nutrients and enjoyment provided by these traditional foods.

Because the WHO PTWI and suggested tolerance cut-off levels for tissue concentrations are based upon information on cadmium representing qualitatively and quantitatively different exposures than through the Arctic and subArctic food chain, the Alaska Division of Public Health recommends that selected research projects be conducted with input, guidance, participation, and final approvals from Alaska Native communities and representatives in collaboration with experts in cadmium research and public health. The goal of these projects is to supplement existing knowledge on the nature, extent and implications of cadmium exposure in Alaska so that relevant information will be available to guide the ongoing evaluation of the safety of subsistence foods in Alaska for populations wishing to maintain a traditional diet. Culturally appropriate communication programs designed to empower individuals and communities to make healthy food consumption choices are also encouraged.

Cadmium

Background

Cadmium is a naturally occurring element in the earth's crust and is distributed at low levels throughout the environment. In water from the open ocean, cadmium concentrations are low varying between 0.02 and 0.1 μg/l. Also, coastal sea and fresh water usually have cadmium levels less than 0.1 μg/l. In areas where there are cadmium and zinc mineral formations, water levels are known to exceed 0.1 μg/l

(Elinder 1992). Cadmium concentrations in soil usually range from 0.1 to 1 ppm, but soils found in areas of phosphate rock can contain up to 100 ppm cadmium (Elinder 1985; Gamberg et al. 1994).

Global pollution from cadmium has resulted from industrial sources. Coal burning, metal mining and refining processes, fertilizers, and waste water are some of the human activities or products that have resulted in the release of cadmium into the environment (ATSDR 1993). Concern regarding cadmium intake has focused on plant foods grown in polluted areas, particularly rice in Japan (Watanabe et al. 1989), and vegetables grown near sources of pollution in Europe (Sherlock et al. 1984; Dollard et al. 1989; Thornton 1992).

For the general US population, food and cigarette smoke are the primary sources of cadmium exposure. Average cadmium levels in cigarettes range from 1.0 to 3.0 parts per million (ppm, or μg/g) (ATSDR 1993). Cadmium concentrations in dairy products, fish, and beef normally contain less than 0.01 ppm (wet weight); fruits, vegetables, and grains contain concentrations usually ranging from 0.01 to 0.1 ppm (Elinder 1992); and the liver and kidneys of domesticated cattle contain cadmium concentrations typically ranging from 0.1 to 1.0 ppm (wet weight) (Elinder 1992). The liver of some crustaceans represent a large proportion of the edible meat, and levels of cadmium can vary greatly depending upon the age and species of shellfish, and location. Oysters and mussels typically have higher cadmium concentrations than other forms of shellfish and levels can range widely from 0.2 ppm to 30 ppm (wet weight) (Elinder 1985; FDA et al. 1993; Gamberg et al. 1994). Even

within the oyster family, different species taken from the same waters can have markedly different cadmium concentrations, such as the higher cadmium concentrations noted in Bluff oysters (*Tiostrea lutaria*) compared to rock oysters (*Crassostrea glomerata*) from the New Zealand coast (Nielsen et al. 1975).

In the Arctic, certain plants such as lichen take up cadmium that is naturally present in soils and deposited from distant industrial sources. Animals that graze on the lichen and other plants may accumulate cadmium in their liver and kidneys. In a similar manner, cadmium enters the aquatic food chain, accumulates in tissues, particularly liver and kidneys and biomagnifies in the food chain.

Marine and Terrestrial Mammals in Alaska

Liver and kidney of subsistence species in Alaska and other Arctic areas are known to contain relatively high amounts of cadmium (Byrne et al. 1985; Bratton et al. 1990; Becker et al. 1995; OHara et al. 1996). Because cadmium accumulates in the liver and kidneys over time, older aged animals have higher concentrations than younger animals. A summary of published reports from Alaska and other Arctic areas depict a wide range of cadmium concentrations in kidney and liver of marine mammals (Ponce et al. 1996 Tables 1-2). Data provided by the US Fish and Wildlife Service of walrus from Gambell and Savoonga showed walrus liver cadmium levels ranging from 1.4 to 50 μg/g (ppm), wet weight, with a mean of 9.4 ppm and a median of 6 ppm (US Fish and Wildlife Service). Of 65 livers tested, 10 exceeded 15 ppm and 4 exceeded 20 ppm (Figure 1). The walrus data and data from

other studies suggest that levels of cadmium in liver and kidney are highly skewed for wildlife species in general.

Published Canadian data and unpublished Alaska data on caribou indicate similar or lower tissue liver and kidney cadmium concentrations in caribou compared to marine mammals. An unpublished report of caribou sampled in northern Alaska, showed average liver cadmium concentrations of 0.7 ppm (ranging from 0.14 to 1.60) and average kidney concentrations of 3.32 ppm (ranging from 1.97 to 6.13) (wet weight) (OHara 1995). In a Canadian report, cadmium levels in the Porcupine (Yukon Territory), Beverly (near the Great Slave Lake of NW Territories), and Southamptom herds (Island, Hudson Bay) were similar and therefore combined into one analyses (Gamberg et al. 1994). Mean whole liver and renal cortex cadmium concentrations increased with age and were comparable to concentrations by age in caribou sampled in Norway (Figure 2 and 3). It should be noted that the data depicted are of renal cortex cadmium concentrations which would be higher than levels measured in homogenized whole kidney. The Canadian and Norwegian data presented are comparable to the range of values reported from Northern Alaska (OHara 1995). The data illustrate the importance of considering factors such as age of animal tested when comparing cadmium tissue concentrations over time within or between herds. No reports of cadmium tissue concentrations on other ungulates in Alaska were identified.

In most wildlife reports from Alaska and other Arctic areas, age information on the animals tested is usually missing, and summary data are usually presented as means not medians. The mean provides misleading information about the average concentration of cadmium in organ meats if the data are skewed as depicted in Figure 1. The lack of age information, the small number of Alaska studies, and the small number of tissues sampled in Alaska make it difficult to make meaningful comparisons of average tissue concentrations between Alaska and other geographic areas. For example, mean ringed seal kidney based on 29 samples in Greenland was 37.4 μg/g (wet weight) compared to a mean of 5.13 μg/g in Alaska based on two animal samples (Johansen et al. 1980; Becker et al. 1995). Also, these limitations in the data make it difficult to accurately predict the range of likely exposures to cadmium through the consumption of these species.

Age or a proxy measure of age can help provide information about whether a new source of pollution is present in the environment. For example, if young animals have the same or higher tissue concentrations as older member of their species, this could be valuable information in identifying a potential source of pollution in the area. While future monitoring efforts are needed, field studies need to include, at a minimum, age or a proxy measure of age to better evaluate the environment, detect changing patterns in tissue concentrations, and compare geographic areas.

Shellfish

Limited data are available regarding the cadmium content of shellfish in Alaska. In a preliminary assessment, the Alaska Department of Environmental Conservation (AKDEC) monitored shellfish from December 1995 to June 1996 (Barrett 1996). The average cadmium concentrations for each species of crab, mussel, clam, and oyster fell below 3.7 μg/g (ppm), which is

the suggested Food and Drug Administration's tolerance level of concern for shellfish (FDA et al. 1993). In certain species, however, the maximum concentrations of cadmium exceeded the 3.7 ppm tolerance level. For example, of 14 Blue mussels tested, the mean concentration was 1.4 ppm, with values ranging from 0.105-10.15 ppm; for 44 oysters tested, the mean concentration was 3.25 ppm, with values ranging from 0.78-5.92 ppm.

Health Effects of Cadmium

Unlike essential elements, cadmium has no known essential usefulness in humans, animals or plants. Eating or breathing cadmium over a lifetime will build up the cadmium levels of the kidneys and liver. The kidney is the most critical organ in which chronic cadmium exposure and resulting damage first occurs. Most orally ingested cadmium passes through the gastrointestinal tract, is excreted in the feces, and is not absorbed (Kjellstrom et al. 1978). Cadmium absorption from food has been estimated to be about 3-7% in humans (Morgan et al. 1984; Elinder 1992). Cadmium absorption is considerably higher for inhaled cadmium than ingested cadmium, with estimates of absorption ranging from 10 to 60% (Elinder 1992). The amount of inhaled cadmium that is absorbed depends upon the chemical solubility of the Cd and the particle size, which determines the location and extent of deposition in the lungs. It is estimated that up to 50% of small particles (<0.1 micron) inhaled will be deposited in the alveoli, and that between 50-100% of the deposited cadmium in the alveoli is ultimately absorbed (Nordberg et al. 1985). The very small size of particles in cigarette smoke results in a high deposition of the particles in the alveoli and a high bioavailability of

the inhaled cadmium (Nordberg et al. 1985). Persons who smoke one pack per day will usually have blood cadmium levels twice as high as those of nonsmokers. Inhaled cadmium, over a long period of time, could result in chronic respiratory dysfunction and may increase one's risk of lung cancer. Evidence for these health effects are based largely upon the occupational studies of workers and laboratory animals exposed to cadmium dust or fumes (ATSDR 1993).

Whether exposure is through inhalation or ingestion, once cadmium is absorbed it accumulates in the body and is eliminated slowly, with a biological half-life estimated to be 14-38 years in humans (Kjellstrom et al. 1971; Tsuchiya et al. 1972). Thus, cadmium body burdens increase with age. Approximately one-third to half of the body burden of cadmium is concentrated in the kidney, with the greatest concentrations occurring in the renal cortex (Syversen et al. 1976; Anke et al. 1979). In older individuals, however, more cadmium may be excreted than among younger individuals because of age- or disease-related decreases in the ability of the kidneys to reabsorb and store circulating cadmium (Sartor et al. 1992). In the absence of renal tubular damage, however, cadmium body and kidney burdens continue to increase with age (Takebayashi 1980).

When humans develop kidney damage, the first clinical indication is decreased proximal tubule reabsorption, resulting in an increase in urinary excretion of low molecular weight proteins, including metallothionein, B_2-microglobulin, immune globulin chains, and enzymes (i.e., muraminidase and ribonuclease). With high and prolonged exposures, cadmium can lead

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to severe kidney failure. While urinary B_2-microglobulin is an indicator of general renal status, urinary metallothionein is a useful indicator of cadmium body burdens (Kjellstrom et al. 1977). However, urinary metallothionein excretion is also induced by other metals, such as zinc and copper (Shaikh et al. 1984) which are also present in organ tissues.

In addition to renal damage, ingested cadmium has been related to other effects in animal studies and in acute, high-dose poisoning episodes in humans. The effects include hepatic and teratogenic effects, and under unique nutritional circumstances, in Japan and among occupationally exposed workers, skeletal disease: osteoporosis and osteomalacia (Friberg et al. 1986; Kjellstrom 1992). These effects occur at extremely high exposure levels that far exceed exposure levels through the diet.

Cadmium acetate is related to hypertension in animal studies (Schroeder 1965; Schroeder 1967), but there is little evidence for an association in humans based on studies of workers, hypertensive patients, or of groups of individuals exposed to low doses of cadmium (Staessen et al. 1984; Elinder 1985; Kromhout et al. 1985).

Background on the Scientific Information Upon Which Food Consumption Guidelines Are Based

Considerable information about cadmium comes from the Itai-Itai disease outbreak associated with the consumption of rice contaminated by cadmium from polluted irrigation water in Japan. (Unfortunately, the chemical form of cadmium has not been provided in the published literature.) The intake of cadmium by Itai-Itai patients has

been estimated to be about 600 μg or more per day over a prolonged period of time (Yamagata et al. 1970). After 20 years, this diet could produce high renal cortex cadmium levels (>400 ppm). The Japanese Itai-Itai patients, however, also suffered from nutritional deficiencies in iron, calcium and protein (Nomiyama et al. 1973; Commission of the European Communities 1978). Since these nutritional deficiencies are known to increase absorption of cadmium and because iron deficiency may exacerbate cadmium nephrotoxicity, the nutritional status of the Itai-Itai patients may have contributed to cadmium absorption and/or toxicity.

Based on all available data from Japan, a no-effect level of cadmium was suggested to be approximately 200 μg Cd ingested per day (or an average of 1,400 μg per week) for the average adult. A daily intake of 200 μg a day for 50 years would provide a theoretical renal cortex concentration of 364 μg/g (ppm) (Friberg et al. 1974; Commission of the European Communities 1978). It should be noted that Friberg and colleagues concluded that it was impossible to use the Japanese data to definitively determine the no-effect level of cadmium.

Based on Friberg's information and synthesis of the data, the joint FAO/WHO Expert Committee on Food Additives proposed a provisional tolerable weekly intake (PTWI) of 400 to 500 μg of cadmium for an average size person weighing 70 kg, which translates to an average daily intake of 57 to 71 μg per day (WHO 1972; Commission of the European Communities 1978). The WHO PTWI corresponds to 28-35% of the theoretical no-effect level of cadmium based on the Japanese data. Thus, the provisional guidelines incorporate a

margin of safety, assuming that the theoretical calculations of a no-effect level are accurate.

The US Food and Drug Administration (FDA), based on the Japanese cadmium data, suggested comparable exposure guidelines, with a maximum tolerable daily intake of 55 μg of cadmium per person per day (FDA et al. 1993). The calculations were based upon the assumption that the bioavailability of the ingested cadmium in the industrial contamination leading to the Itai-Itai outbreak was similar for cadmium in shellfish. A total cadmium level of concern for shellfish was determined by dividing the tolerable daily intake (i.e., 55 μg) by the daily intake of shellfish for the top 10th percentile of shellfish consumers (i.e., 15 grams) based on a food frequency survey conducted by the Market Research Corporation of America (FDA et al. 1993). Thus, the tolerance level for shellfish was calculated as 3.7 ppm. A similar process was used to calculate the tolerance level for kidney (3.0 ppm) and liver (1.0 ppm) (Spierenburg et al. 1988).

Dietary Intake of Liver and Kidney and Risk Assessment

Limited data are available regarding the extent of liver and kidney consumption in Alaska. In a dietary survey of Siberian Yupiks, who are known to rely heavily upon traditional foods, 10 out of 79 survey respondents indicated consuming liver or other organ meats at least once a week within the past year (Nobmann 1997). In a food recall survey of 359 people in 11 communities conducted between 1987 and 1988, there were 2,069 mentions of meat, fish, game bird or poultry servings consumed within the past 24 hours, of which there were a total of 17 mentions of any type of liver or other organ meat servings consumed (0.8%) (Nobmann 1989). These data suggest that liver or kidney consumption may not be common in the 11 communities surveyed: Anchorage, Sitka, Kake, Dillingham, Pedro Bay, Pilot Point, Bethel, Kwigillingok, Mt. Village, and Kotzebue. Although insufficient information exists, geographic and seasonal variation in liver, kidney and other organ meat consumption is likely. It should be noted that villages that rely heavily upon marine mammals were not part of the dietary survey (e.g., Wales, Little Diomede, Savoonga and Gambell, Kaktovik, Barrow, Wainwright, and Pt. Hope).

In the Yukon Territories, a risk assessment for caribou kidney indicated that a meal of caribou kidney cortex every week would result in an exceedance of the PTWI of 500 μg of cadmium per week. However, because one caribou provides a substantial number of meals for a hunter and family, but only a limited number of meals of kidney and liver, and because the PTWI assumes weekly exposures, every year, over a lifetime, the Government of the Northwest Territories issued a health communication message stating that "caribou organs were safe to eat in unlimited quantities" (Northwest Territories Renewable Resources 1995).

For large marine mammals, an entire village will share in the harvest, so that large kidneys and liver would be distributed over an entire population rather than one household. However, for some marine mammals the size of these organs are quite large. Seasonal variation with higher and more frequent consumption of liver and kidney during the whaling seasons is likely.

The mean Cd tissue concentrations of common food items in US markets and in species traditionally harvested and consumed are presented in Table 3. Alaska Bowhead whale muscle and blubber tissues and several species of clams in Alaska show low levels of Cd tissue concentrations, with average concentrations less than or equal to 0.10 ppm. Also, US clams and oysters (FDA et al. 1993), and US fruits, vegetables and grains have average concentrations usually ranging from 0.01 to less than 0.10 ppm (Elinder 1992). For an average weight 70 kg adult the lifetime weekly intake of 11 pounds or 5,000 grams of food items containing an average Cd concentration of 0.10 ppm would provide the WHO PTWI.

Caribou from Northern Alaska (OHara 1995) have average liver cadmium concentrations (<1.00 ppm) comparable to those of US domestic cattle (Elinder 1992), Norwegian moose (Gamberg et al. 1994), Canadian musk oxen (Gamberg et al. 1994), and numerous species of clams in Alaska (Barrett 1996). A lifetime weekly intake of 1.1 pounds of food items containing an average Cd concentration of 1.00 ppm would provide the WHO PTWI.

The limited data on pacific oysters (Barrett 1996), beluga and ringed seal liver (Becker et al. 1995), and caribou kidney from Alaska (OHara 1995) identified average Cd tissue concentrations ranging from greater than 1.0 ppm to 3.5 ppm. For species with average tissue concentrations of 3.5 ppm, the lifetime consumption of a third a pound a week of these above food items would provide the WHO PTWI.

Species and tissues with particularly high mean Cd concentrations were pacific walrus kidney and bowhead whale kidney, with mean tissue levels exceeding 20 ppm (Tables 1 & 2). Lower concentrations were observed in the liver of walrus and bowheads and in beluga kidney ($\leq$ 12 ppm). A lifetime weekly consumption of one-tenth of a pound of food containing 12.0 ppm Cd would provide the WHO PTWI (Table 3).

Because the WHO PTWI of 500 μg is 35% of the theoretical no-effect level of cadmium (i.e., 1,400 μg per week), considerably greater amounts of food could be consumed than those presented in table 3. For example, for tissues with mean Cd concentrations of 0.1 ppm, the WHO PTWI would correspond to 11 pounds of food consumed per week, whereas 31 pounds would need to be consumed each week over a lifetime to reach the theoretical no-effect level of cadmium in the kidney. Similarly, for food items with mean Cd tissue concentrations of 3.5 ppm, only one-third of a pound provides the WHO PTWI, whereas 1 pound of these food items would need to be consumed weekly over a lifetime to reach the theoretical no-effect level. Likewise, for food items containing Cd tissue concentrations of 12.0 ppm, less than two ounces provides the WHO PTWI, whereas one quarter of a pound a week over a lifetime would be needed to provide the theoretical no-effect level of cadmium in the kidney.

Nature of dietary cadmium exposure through ingestion of liver and kidney

Dietary exposure to cadmium occurs along with dietary exposure to a complex array of vitamins, fats, proteins, minerals, trace elements, electrolytes, and fiber: some of which may modify the absorption and/or toxicity of cadmium. Selenium, for

example, is an essential element in the human diet, and liver and kidney of marine mammals are rich sources of selenium. Selenium may prevent many aspects of cadmium toxicity (Parizek et al. 1974). In high-dose laboratory animal studies, cadmium's effect on male gonads (testicular necrosis) (Kar et al. 1960; Mason et al. 1964; Mason et al. 1967) and on the mortality of laboratory rats was greatly reduced by the administration of selenium (Parizek et al. 1974; Gamberg et al. 1994). Also, cadmium-induced effects on laboratory animal ovaries, placenta, and pregnancy were reduced by selenium (Parizek et al. 1968; Gamberg et al. 1994). There is also evidence that iron may reduce the nephrotoxicity of cadmium. While zinc may also reduce cadmium toxicity (Walsh 1985), we identified insufficient information on zinc's possible antagonistic influence on cadmium toxicity in the literature.

While many questions remain regarding the antagonistic effects of selenium, iron, zinc and potentially other elements in cadmium toxicity, the composition of diet and nutritional status is known to influence the extent of cadmium absorption. For example, dietary intake of vitamin D, protein, fiber, zinc, iron, copper, and calcium is known to reduce Cd absorption (Friberg et al. 1974; Flanagan et al. 1978; Fox 1979; Nordberg et al. 1985; Berglund et al. 1994; Vahter et al. 1996). The nutrient composition of liver and kidney of species traditionally harvested in Alaska have not been comprehensively characterized. However, liver, in general is known to contain varying quantities of vitamin D (depending upon the species), and liver is considered an excellent source of protein, zinc, iron, and selenium (Nobmann 1993). Also, kidneys, in general, are known to be a source of protein and trace elements.

In addition to the nutritional aspects of the subsistence diet and organs, cadmium in mammal liver and kidney is mostly bound to a protein called metallothionein (or a metallothionein-like protein) and is not as bioavailable (at least to the liver) as cadmium in its unbound state (Groten et al. 1990; Goyer 1991). For example, in a rat feeding study one group of rats was fed cadmium chloride and another group of rats was fed pigs' livers containing cadmium, 90% of which was bound to metallothionein. While both groups of rats were fed the same amount of cadmium, the liver fed rats had half the uptake of cadmium in their livers as the group fed cadmium chloride, but both groups had comparable levels of cadmium in their kidneys. However, the cadmium chloride group showed more pronounced cadmium-induced changes than the rats eating pigs' livers (Groten et al. 1990).

Considerable uncertainty remains, however, regarding the factors that determine the level of cadmium-metallothionein (Cd-MT) which may be toxic and the role of MT-bound cadmium in renal toxicity. Animal experiments suggest that Cd-MT administered orally is distributed proportionally more to the kidney than orally administered cadmium ions (Cherian 1983). MT-bound cadmium in blood plasma is filtered through the glomeruli and taken up by tubular reabsorption in the renal tubule (Nordberg et al. 1985). Cadmium enters the lysosomes of the tubular cells where MT is degraded and "free" cadmium is released and able to react to sensitive sites in the cell (Fowler et al. 1978). Free cadmium would, in turn, induce the synthesis of MT which, in turn, would potentially increase the resistance of the kidney to cadmium exposure (Nordberg et al. 1992). For example, the toxic effects (tubular dysfunction) of high doses of Cd-

MT in laboratory animals was prevented by pretreatment with small non-toxic doses of cadmium (Jin et al. 1987a; Jin et al. 1987b). In addition, in high-dose short-term animal experiments, lower kidney cadmium levels were related to histologic signs of damage (10 μg/g) than in animal experiments using long-term low-level exposures (130 μg/g) in the same animal species (Nordberg et al. 1975). Thus, it is believed that intracellular binding of cadmium to MT protects the renal cortex (Nordberg et al. 1992). Also, differences in intracellular cadmium binding may explain the different levels of total cadmium related to damage in the renal cortex. Intracellular binding to MT may also help explain why certain species, such as penguins in Antarctica (Elinder 1992), appear to tolerate extremely high levels of kidney cadmium burdens. Histopathologic studies of kidneys from different species known to have high cadmium levels may be worthwhile in understanding the implications of chronic exposure to cadmium through the marine food chain.

Human Studies in the Arctic

There have been a number of studies in the Arctic which have characterized cadmium exposure. Because of the high level of cadmium identified in the liver and kidney of seals and other subsistence species represented in the Greenlandic diet, the WHO Provisional Tolerable Weekly Intake was estimated to be routinely exceeded by a factor of 10 in areas with traditional diets (Johansen et al. 1980). However, blood levels of cadmium in Greenland were similar to those observed in Denmark where exposures to dietary cadmium are considerably lower (Hansen et al. 1985). Similarly, in a study of Swedish non-smoking women, blood cadmium levels

were similar between those eating a diet containing shellfish and those eating a low shellfish diet, despite a two-fold difference in dietary cadmium intake (Vahter et al. 1996). Similar findings have been observed among oyster eaters in New Zealand (Sharma et al. 1983; McKenzie-Parnell et al. 1988). In Canada, a study examining blood cadmium levels identified a 10-20 fold higher level of cadmium among cigarette smokers compared to non-smokers, but no differences were observed between Inuit and urban and rural Caucasian study participants (Benedetti et al. 1994).

In another study, the cadmium concentration of the renal cortex of autopsied individuals from the Faroe Islands was compared to autopsied individuals from Bergen, Norway (Julshamn et al. 1989). No differences in cadmium tissue levels were observed despite the fact that the Faroe Islanders were known to have high cadmium intake through the heavy consumption of pilot whale meat. Unfortunately, however, the study did not control for smoking histories among the individuals autopsied.

In Alaska, the State's Division of Public Health examined urine and blood among 10 elderly residents of St. Lawrence Island in October, 1986. The participants were known to have a lifetime history of whale, seal and walrus liver and kidney meat consumption (Middaugh et al. 1986). Blood and urine was collected for cadmium analyses and urine for B_2-microglobulin, an early marker for renal damage. Blood and urine cadmium levels were low (all below 5 ng/ml which is considered normal), and urine levels of B_2-microglobulin levels were normal or slightly elevated, reflecting the advanced ages of many of the study participants.

Because the available epidemiologic data are limited, additional human biomonitoring would be helpful in characterizing the extent of cadmium exposure, particularly if data were collected with assessments of dietary intake and cadmium concentrations in eaten meals. Well designed epidemiologic studies could help evaluate the implications of iron deficiency (which is common in Alaska Natives) which occurs despite the high dietary intake of iron. While iron deficiency would enhance cadmium absorption, the high dietary intake of iron would have the opposite effect.

Summary

The monitoring data on tissue concentrations suggests that lifetime weekly consumption of kidney and, to a lesser extent liver, of selected species would provide cadmium exposures exceeding the WHO PTWI. However, the WHO PTWI incorporates a margin of safety, assumes that the weekly amount consumed is consumed every week, every week of the year over a lifetime, and is based largely upon the contaminated rice episode in Japan. For species traditionally harvested in Alaska, the margin of safety incorporated in the WHO PTWI may potentially be made even larger by the fact that liver and kidney meats and shellfish are rich in elements known to reduce cadmium absorption and/or toxicity.

Thus, based on all of the available information described in this document, and the nutritional and cultural value of foods traditionally harvested and consumed, the Division of Public Health fully supports the consumption of kidney and liver from subsistence species as part of a varied and well-balanced diet. Organ meats are a rich source of protein, vitamins, essential elements, and calories. For example, one 9-ounce serving of moose liver provides all the vitamin C needed for a day. People wishing to enjoy their traditional foods should continue to do so.

For those wishing to reduce their cadmium exposures, choosing a well-balanced diet which includes meals rich in calcium, fiber, protein, and iron will help reduce cadmium absorption. Also, limiting the consumption of kidney and liver from older marine mammals or simply choosing a liver meal over a kidney meal would be an effective way to reduce cadmium exposures without losing the nutrients and enjoyment associated with the consumption of these organs. Most importantly, for individuals that smoke cigarettes, cadmium exposures can be significantly reduced by limiting or quitting cigarette smoking.

Further work could help promote a better understanding of the nature and implications of cadmium exposure in Alaska so that advice can be based upon information relevant to Alaska and other Arctic areas. Selected research projects could be developed with input, guidance, and final approval from Alaska Native communities and representatives. Examples of selected projects include:
- the characterization of cadmium exposure and early markers of renal effects (through urine analysis for proteinuria) among individuals with a lifelong history of organ consumption;
- laboratory animal studies about the fate and effects of ingested Cd-MT;
- laboratory animal studies about the influence of the combination of elements common in food items (such as selenium, zinc, and iron) on cadmium's nephrotoxicity;

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- ongoing trace metal monitoring of liver and kidney of subsistence species with a greater emphasis on collecting age information of animals tested;
- histopathologic studies of subsistence species with high tissue cadmium concentrations;

- comprehensive research on the nutrient value of all traditional foods, including liver and kidney;
- exploration of techniques to enable the incorporation of information on nutrient composition of food in the risk assessment process.

Table 1.   Cadmium levels (μg/g, wet weight) in bowhead whale from published literature

Reference	Date Collected	Sampling Location	Tissue	Cadmium Mean (μg/g), ww	SD	N
Bowhead Whale						
(Byrne et al. 1985)	1979-80	Alaska	B	.03	.04	7
(Bratton et al. 1990)	1986	Alaska	B	.03	.04	6
(Bratton et al. 1990)	1988	Alaska	B	.06	.03	4
(Byrne et al. 1985)	1979-80	Alaska	K	1.42		2
(Bratton et al. 1990)	1986	Alaska	K	6.56	1.76	6
(Bratton et al. 1990)	1988	Alaska	K	15.30	2.84	4
(Bratton, et al. 1995[a])		Alaska	K	21.23		
(Byrne et al. 1985)	1979-80	Alaska	L	1.50		1
(Bratton et al. 1990)	1986	Alaska	L	7.21	1.69	6
(Bratton et al. 1990)	1988	Alaska	L	12.10	1.79	4
(Becker et al. 1995)	1992-93	Alaska	L	12.90	10.90	3
(Byrne et al. 1985)	1979-80	Alaska	M	.02	.02	2
(Bratton et al. 1990)	1986	Alaska	M	.07	.06	6
(Bratton et al. 1990)	1988	Alaska	M	.08		1

Abbreviations used include: ww, wet weight; B, blubber; K, kidney; L, Liver; M, muscle; Cd, cadmium, N, number of samples; SD, standard deviation Source: (Ponce et al. 1996).

a. Unpublished document as reported in (OHara 1995).

Table 2. Cadmium levels (μg/g wet weight) in beluga whale, bearded seal, harbor seal and walrus from published literature

Reference	Date Collected	Sampling Location	Tissue	Cadmium Mean (μg/g), ww	SD	N
Beluga Whale						
(Becker et al. 1995)	1989-90	Alaska	L	1.99	.93	15
(Hansen et al. 1985)	1980	Greenland	L	.01		40
(Hansen et al. 1985)	1980	Greenland	K	.01		36
(Hansen et al. 1985)	1980	Greenland	M	.01		41
(Tarpley, 1995[a])		Alaska	K	11.6		
Bearded Seal						
(Becker et al. 1995)	1989-93	Alaska	L	1.03	.99	3
Harbor Seal						
(Miles et al. 1992)	1976-78	Alaska	K	6.60	6.60	23
Pacific Walrus						
(Taylor et al. 1989)	1981-84	Alaska	K	46.50	20.20	42
(Miles et al. 1992)	1981-84	Alaska	L	9.47	8.26	65
(Eisler, 1985[a])		Alaska	K	51.6		
(Seagers, 1995[a])		Alaska	K	27.9		
Ringed Seal						
(Becker et al. 1995)	1989-93	Alaska	K	5.13	5.13	2
(Fallis, unpubl. in Muir et al., 1992)	1977	Canada	K	2.79		1
(Johansen et al., 1980 in Muir et al., 1992)	1979	Greenland	K	37.40	33.70	29
(Becker et al. 1995)	1989-93	Alaska	L	2.33	2.32	14
(Fallis, unpubl. in Muir et al., 1992)	1975	Canada	L	4.20	3.30	5
(Fallis, unpubl. in Muir et al., 1992)	1977	Canada	L	5.50	.08	5
(Johansen et al., 1980 in Muir et al., 1992)	1979	Greenland	L	7.32	3.00	29
(Fallis, unpubl. in Muir et al., 1992)	1975	Canada	M	.03	.02	6
(Fallis, unpubl. in Muir et al., 1992)	1977	Canada	M	.05	.01	7
(Johansen et al., 1980 in Muir et al., 1992)	1979	Greenland	M	.07	.10	29

Abbreviations used include: ww, wet weight; B, blubber; K, kidney; L, Liver; M, muscle; Cd, cadmium, N, number of samples; SD, standard deviation Source: (Ponce et al. 1996).

a. Unpublished data as reported in (OHara 1995).

Table 3. **Allowable Lifetime Weekly Intake of Food By An Average Weight 70 kg Adult Based Upon Mean Concentrations Of Cadmium (Cd) In Different Food Sources And The World Health Organization's Provisional Tolerable Weekly Intake of 500 μg[1].**

	Average Weekly Allowable Intake Guidelines	
Mean Cd Concentration (μg/g)	grams	pounds
0.01[a]	50,000	110.00
0.10[b]	5,000	11.00
1.00[c]	500	1.10
3.5[d]	143	0.32
7.0[e]	71	0.16
12.0[f]	42	0.10
>20[g]	<25	<0.06

1. Limited sample sizes, the reporting of means not medians in the literature, and the wide range in Cd tissue concentrations observed for some species make accurate assessments of allowable average intakes subject to considerable error.

a. U.S. Fish, dairy and beef products (Elinder 1992).
b. U.S. fruits, vegetables and grains (Elinder 1992), U.S. clams and oysters (FDA et al. 1993), Alaska Bowhead whale muscle and blubber (Table 1), and Alaska cockle and Eastern softshell and red neck clams (Barrett 1996).
c. Average levels of Cd in liver of U.S. domestic cattle (Elinder 1992), Norwegian moose (Gamberg et al. 1994), Canadian Muskoxen (Gamberg et al. 1994), and Northern Alaska caribou (OHara 1995), and Alaska clams (razor, horse, little neck, butter, and geoduck clams) (Barrett 1996) fall under 1.0 ppm.
d. Average Cd levels of Northern Alaska caribou kidney (OHara 1995), Alaska beluga and ringed seal liver (Table 2), and pacific oysters range from 1 to 3.5 ppm (Barrett 1996).
e. Average Cd levels in Alaska harbor and ringed seal kidney (Table 2) are measured below 7.0 ppm.
f. Average Alaska walrus and bowhead liver and beluga kidney concentrations $\leq$ 12 ppm (Table 1 & 2).
g. Average Alaska kidney concentrations for bowhead whale and walrus exceed 20 ppm (Tables 1 & 2).

Figure 1: Cadmium Levels in Walrus Liver, 1981-1984 (N=65)
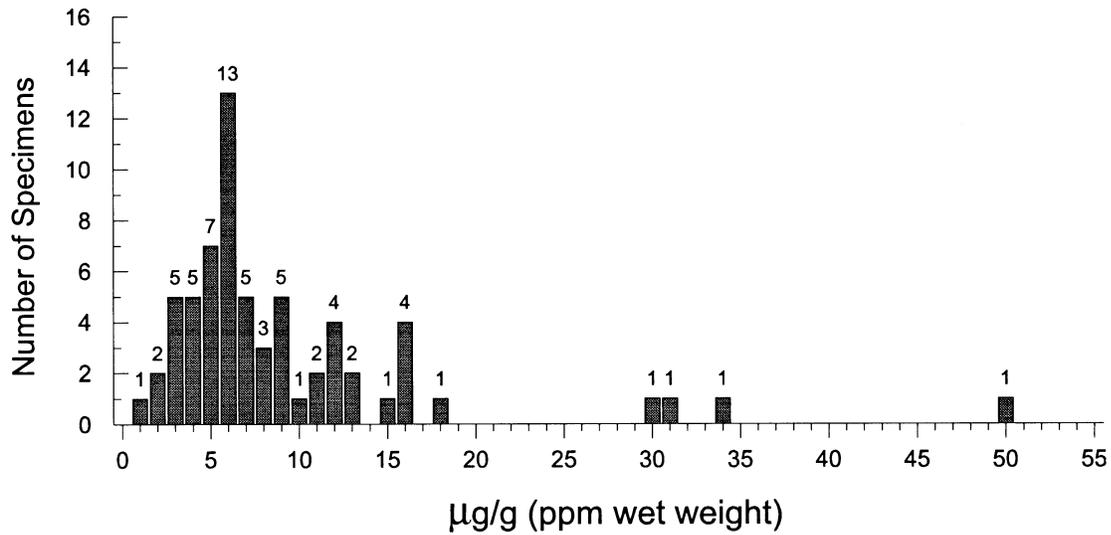
Source: U.S. Fish and Wildlife Service Data, St. Lawrence Island, Alaska.

Figure 2: **Renal Cortex Cadmium Concentrations (μg/g, wet weight) in Canadian and Norwegian Caribou.**
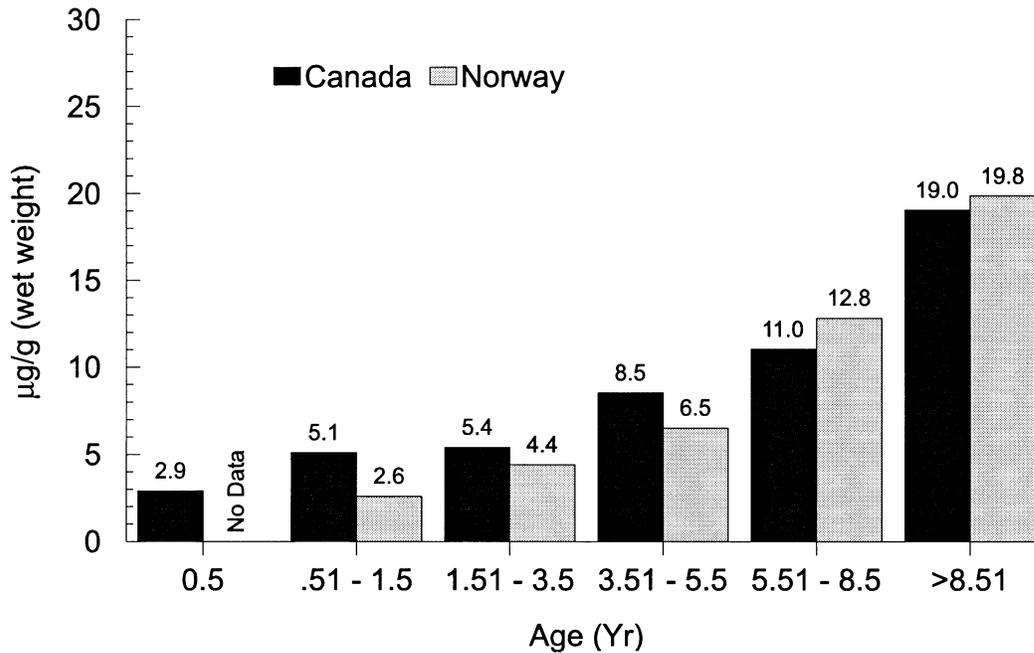
Source: (Gamberg et al. 1994)

Figure 3: **Liver Cadmium Concentrations (µg/g, wet weight) in Canadian and Norwegian Caribou.**
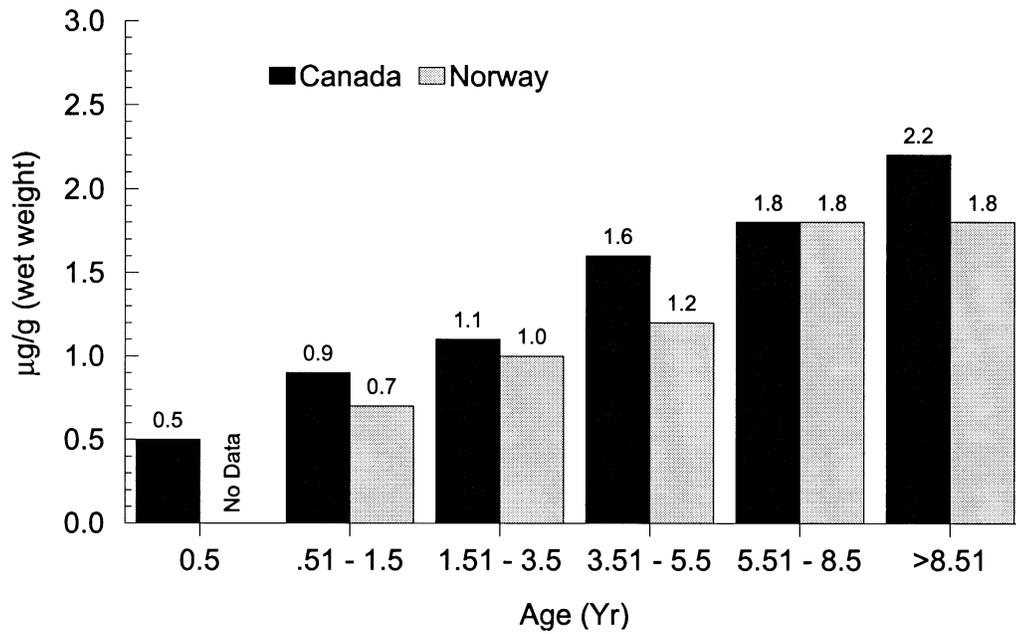
Source: (Gamberg et al. 1994)

References

Anke, M., M. Partschefeld, M. Grun, B. Groppel (1979). The Capacity of Different Parts of the Body to Reflect Cd-Exposure. Kadmium Symposium, Jena, Veroffentlichung der Friedrich-Schiller-Universitat: 242-249.

ATSDR (1993). Toxicological Profile for Selected PCBs (Aroclor-1260, -1254, -1248, -1242, -1232, -1221, and -1016). Atlanta, GA, U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry 209.

Barrett, R.E. (1996). Preliminary report on heavy metal concentrations in Alaskan shellfish: Environmental Health Laboratory, State of Alaska, Department of Environmental Health.

Becker, P.R., E.A. Mackey, M.M. Schantz, R.R. Greenberg, B.J. Koster, S.A. Wise, D.C.G. Muir (1995). Concentrations of Chlorinated Hydrocarbons, Heavy Metals and Other Elements in Tissues Banked by the Alaska Marine Mammal Tissue Archival Project: U.S. DOC, National Institute of Standards and Technology: NISTIR 5620.

Benedetti, J.L., E. Dewailly, F. Turcotte, M. Lefebvre (1994). "Unusually high blood cadmium associated with cigarette smoking among three subgroups of the general population, Quebec, Canada." Sci Total Environ 152:161-167.

Berglund, M., A. Akesson, B. Nermell, M. Vahter (1994). "Intestinal absorption of dietary cadmium in women depends on body iron stores and fiber intake." Environ Health Perspect 102(12): 1058-1066.

Bratton, G.R., W. Flory, B. Spainhour (1990). Environmental Pollutant Levels in Selected Tissues from Subsistence Harvested Bowhead Whales. Fifth Conference on the Biologyu of the Bowhead Whale *(Balaena mysticetus)*, Anchorage, Alaska.

Byrne, C., R. Balasubramanian, E.B. Overton, T.F. Albert (1985). "Concentrations of Trace Metals in the Bowhead Whale." Mar Pollut Bull 16(12):497-498.

Cherian, M.G. (1983). "Absorption and tissue distribution of cadmium in mice after chronic feeding with cadmium chloride and cadmium metallothionein." Bull Environ Contam Toxico 30: 33-36.

Commission of the European Communities (1978). Criteria (Dose/Effect Relationships) for Cadmium: Directorate-General for Social Affairs, Health and Safety Directorate: ISBN 0-08-022024-X, RA1231.C3 77-30193.

Dollard, G.J., T.J. Davies (1989). A Study of the Contribution of Airborne Cadmium to the Cadmium Burdens of Several Vegetable Species: Harwell, United Kingdom Atomic Energy Authority.

Elinder, C.G. (1985). "Other Toxic Effects". Cadmium and Health. A Toxicological and Epidemiological Appraisal, Vol. II, Effects and Response, Boca Raton FL CRC Press: 159-204.

Elinder, C.G. (1992). "Cadmium as an Environmental Hazard". Cadmium in the Human Environment: Toxicity and Carcinogenicity Lyon, International Agency for Research on Cancer IARC: 123-132.

FDA, A.M. Adams (1993). "Methyl mercury in salmon", correspondence.

Flanagan, P.R., J.S. McLellan, J. Haist, G. Cherian (1978). "Increased dietary cadmium absorption in mice and human subjects with iron deficiency." Gastroenterology 74(May):841-846.

Fowler, B.A., G.F. Nordberg (1978). "The renal toxicity of cadmium metallothionein: morphometric and X-ray microanalytic studies." Toxicol Appl Pharmacol 46:609-623.

Fox, M.R.S. (1979). "Nutritional influences on metal toxicity: cadmium as a model toxic element." Environ Health Perspect 29(Apr):95-104.

Friberg, L., C.G. Elinder, T. Kjellstrom, G.F. Nordberg (1986). Cadmium and Health: An epidemiological and Toxicological Appraisal, Vol. II, Effects and Responses. Boca Raton FL, CRC Press.

Friberg, L., M. Piscator, G.F. Nordberg, T. Kjellstrom (1974). Cadmium in the Environment 2nd Edition. Cleveland, Ohio, CRC Press Inc.

Gamberg, M., A.M. Scheuhammer (1994). "Cadmium in caribou and muskoxen from the Canadian Yukon and Northwest Territories." Science of the Total Environment 143:221-234.

Goyer, R.A. (1991). "Toxic Effects of Metals". Casarett and Doull's Toxicology: The Basic Science of Poisons. 4th Edition, New York Pergamon Press.

Groten, J.P., E.J. Sinkeldam, J.B. Luten, P.J. van Bladeren (1990). "Comparison of the toxicity of innorganic and liver-incorporated cadmium: A 4-wk feeding study in rats." Fd Chen Toxic 28:435-441.

Hansen, J., H. Wulf, N. Kromann,K. Alboge (1985). "Cadmium concentrations in blood samples from an East Greenlandic population." Dan Med Bull 32: 277-279.

Jin, T., G.F. Nordberg, M. Nordberg (1987b). "Resistance to acute nephrotoxicity induced by cadmium metallothienein dependence on pretreatment with cadmium chloride." Pharmacol Toxicol 61:89-93.

Jin, T., G.F. Nordberg, N. Nordberg (1987a). "Influence of cadmium metallothienein pretreatment on tolerance of rat kidney cortical cells to cadmium toxicity *in vitro* and *in vivo*." Pharmacol Toxicol 60:345-349.

Johansen, P., F.O. Kapel, I. Kraul (1980). Heavy Metals and Organochlorines in Marine Mammala, C.M. E:32.

Julshamn, K., K. Andersen, O. Ringdal, M. Egholm (1989). "Trace elements intake in the Faroe Islands III. Element concentrations in human organs in populations from Bergen (Norway) and the Faroe Islands." Sci of Total Environ 84:25-33.

Kar, A.B., R.P. Das, B. Mukerji (1960). "Prevention of cadmium-induced changes in the gonads of the rat by zinc and selenium; a study in antagonism between metals in the biological system." Proc Natl Inst Sci India Part B 26:40.

Kjellstrom, T. (1992). "Mechanism and epidemiology of bone effects of cadmium". Cadmium in the Human Environment: Research on Cancer IARC: 301-310.

Kjellstrom, T., K. Borg, B. Lind (1978). "Cadmium in feces as an estimator of daily cadmium intake in Sweden." Environ Res 15:242-251.

Kjellstrom, T., L. Friberg, G. Nordberg, M. Piscator (1971). "Further Considerations on Uptake and Retrntion of Cadmium in Human Kidney Cortex". Cadmium in the Environment, Cleveland, Ohio CRC Press: 140-148.

Kjellstrom, T., K. Shiroisky, P.E. Evrin (1977). "Urinary beta-2-microglobulin excretion among people exposed to cadmium in the general environment. An epidemiological study in cooperation between Japan and Sweden." Environ Res 13:318-344.

Kromhout, D., E.B. Bosschieter, C.D.L. Coulander (1985). "The inverse relation between fish consumption and 20-year mortality from coronary heart disease." N Engl J Med 312(19):1205-1209.

Mason, K.E., J.A. Brown, J.O. Young, R.R. Nesbit (1964). "Cadmium-induced injury of the rat testis." Anat Rec 149:135.

Mason, K.E., J.O. Young (1967). "Effectiveness of Selenum and Zinc in protecting against cadmium-induced injury of the rat testis". Selenium in Biomedicine, Westport CT Avi Publishing: 383.

McKenzie-Parnell, J., T. Kjellstrom, R. Sharma, M. Robison (1988). "Unusually high intake and fecal output of cadmium, and fecal output of other trace elements in New Zealand adults consuming dredge oysters." Environ Research 46:1-14.

Middaugh, J., W. Hlady, S. Jenkerson (1986). Cadmium in Walrus, Health Hazard and Risk Assessment, St. Lawrence Island: Alaska Division of Public Health, Section of Epidimiology.

Miles, A.K., D.G. Calkins, N.C. Coon (1992). "Toxic Elements and Organochlorines in Harbor Seals (*Phoca vitulina richardsi*), Kodiak, Alaska, USA." Bull Environ Contam Toxicol 48:727-732.

Morgan, H., J.C. Sherlock (1984). "Cadmium intake and cadmium in the human kidney." Food Addit Contam 1:45-51.

Nielsen, S.A., A. Nathan (1975). "Heavy metal levels in New Zealand molluscs." N Z J Mar Freshwater Res 9:467-481.

Nobmann, E.A.B. (1993). Nutrient Value of Alaska Native Foods: US Department of Health and Human Services, Indian Health Service, Alaska Area Native Health Service.

Nobmann, E.A.B. (1997). "Personal Communication".

Nobmann, E.D. (1989). Dietary Intakes of Alaska Native Adults 1987-1988: Alaska Area Native Health Service: Final.

Nomiyama, K., Y. Sugata, I. Mupata, S. Nakagawa (1973). "Urinary low-molecular weight proteins in Itai-Itai disease." Environ Res 6:373.

Nordberg, G., T. Kjellstrom, N.M. (1985). "Kinetics and Metabolism". Cadmium and Health: A Toxicological and Epidemiological appraisal. Vol. I. Exposure, dose, and metabolism, Boca Raton FL CRC Press: 103-178.

Nordberg, G.F., R.A. Goyer, M. Nordberg (1975). "Comparative toxicity of cadmium-metallothionein and cadmium chloride on mouse kidney." Arch Pathol 99:192-197.

Nordberg, M., T. Jin, G.F. Nordberg (1992). "Cadmium, Metallothionein and Renal Tubular Toxicity". Cadmium in the Human Environment: Toxicity and Carcinogenicity Lyon, International Agency for Research on Cancer IARC:293-297.

Northwest Territories Renewable Resources (1995). Environmental Contaminant Study in Caribou: Wildlife Management Division, Department of Renewable Resources, Government of the Northwest Territories.

OHara, T.M. (1995). "Unpublished data on cadmium concentration in caribou tissues". Barrow AK, North Slope Borough Wildlife Management.

OHara, T.M., A. Fairbrother (1996). Risk Assessment of Cadmium in Selected Arctic Wildlife of Northern Alaska. Tenth International Congress on Circumpolar Health, Anchorage, Alaska.

Parizek, J., J. Kalouskova, A.A. Babicky, J. Benes, L. Pavlik (1974). "Interection of Selenium with Mercury, Cadmium and Other Toxic Metals". Trace Element Metabolism in Animals, Baltimore University Park Press. 2:119.

Parizek, J., I. Ostadalova, J. Benes, A. Babicky (1968). "Pregnancy and trace elements: the protective effect of compounds of an essential trace element - selenium - against the peculiar toxic effects of cadmium during pregnancy." J Reprod Fert 16:507-509.

Ponce, R.A., G.M. Egeland, J.P. Middaugh, P.R. Becker (1996). Twenty Years of Trace Metal Analyses of Marine Mammals: Evaluation and Summation of Data from Alaska and Other Arctic Regions. ProceedingsTenth International Conference on Circumpolar Health, in press.

Sartor, F., D. Rondia, F. Claeys, J.P. Buchet (1992). "Factors Influencing the Cadmium Body Burden in a Population Study". Cadimum in the Human Environment: Toxicity and Carcinogenicity Lyon, International Agency for Research on Cancer IARC:101-106.

Schroeder, H.A. (1965). "Cadmium as a factor in hypertension." J Chron Dis 18:647-656.

Schroeder, H.A. (1967). "Cadmium, chromium, and cardiovascular disease." Circulation 35:570-582.

Shaikh, Z.A., L.M. Smith (1984). "Biological indicators of cadmium exposure and toxicity." Experientia 40:36-43, 124-130.

Sharma, R.P., L.M. Smith (1983). "Cadmium in blood and urine among smokers and non-smokers with high cadmium intake via food." Toxicology 29:163-171.

Sherlock, J., J. Hislop, D. Newton, G. Topping, K. Whittle (1984). "Elevation of mercury in human blood from controlled chronic ingestion of methylmercury in fish." Hum Toxicol 3(2):117-31.

Spierenburg, T.J., D.G.G.J., A.J. Baars, D.H.J. Brus, M.J.M. Tielen, B.J. Arts (1988). "Cadmium, zinc, lead, and copper in livers and kidneys of cattle in the neighbourhood of zinc refineries." Environmental Monitoring and Assessment 11:107-114.

Staessen, J., C.J. Bulpitt, H. Roels, B.A., F.R., J.V. Joossens, R. Lauwerys, P. Lijnen, A. Amery (1984). "Urinary cadmium and lead concentrations and their relation to blood pressure in a population with low exposure." Br J Ind Med 41:241-248.

Syversen, T.L.M., T.L. Stray, G.B. Syversen,J. Ofstad (1976). Scand J Clin Lab Invest 36:251.

Takebayashi, S. (1980). "First Autopsy Case, Suspicious of Cadmium Intoxication, From the Cadmium-Polluted Area in Tsushima, Nagasaki Prefecture". Cadmium-Induced Osteopathy, Tokyo Japanese Public Health Association:124.

Taylor, D.L., S. Schliebe, H. Metsker (1989). "Contaminants in blubber, liver, and kidney tissue of Pacific walruses." Mar Pollut Bull 20(9):465-468.

Thornton, I. (1992). "Sources and Pathways of Cadmium in the Environment". Cadmium in the Human Environment: Toxicity and Carcinogenicity Lyon, International Agency for Research on Cancer IARC:149-162.

Tsuchiya, K., Y. Seki, M. Sugita (1972). 17th International Congress Occupational Health, Buenos Aires, Argentina, **Secretariat**.

US Fish and Wildlife **Service** "Unpublished data".

Vahter, M., M. Berglund, B. Nermell, A. Akesson (1996). "Bioavailability of cadmium from shellfish and mixed diet in women." Toxicol Appl Pharmacol 136(2):332-341.

Walsh, P.M. (1985). The Use of Seabirds as Monitors of Heavy Metals in the Marine Environment CRC Press:183-204.

Watanabe, T., H. Nakatsuka, M. Ikeda (1989). "Cadmium and lead contents in rice available in various areas of Asia." Sci Total Environ 80:175-**184**.

WHO (1972). Evaluation of Certain Food Additives and the Contaminants Mercury, Lead and Cadmium, Sixteenth Report of the Joint FAO/WHO Expert Committee on Food Additives: World Health Organization: Technical Report 505.

Yamagata, N., I. Shigematsu (1970). "Cadmium pollution in perspective." Bull Inst Public Health 19:1.

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Risks in Perspective - Polychlorinated Biphenyls (PCBs) and other Polyhalogenated Diaromatic Hydrocarbons

Executive Summary

Polyhalogenated diaromatic hydrocarbons (PHDHs) such as polychlorinated biphenyls (PCBs), dibenzo-*p*-dioxins (PCDDs) and dibenzofurans (PCDFs) are lipophilic, persistent, man-made chemicals. While the manufacture of PCBs has been banned for several decades in many industrial nations, trace amounts of PCDDs and PCDFs continue to be unintentionally produced during some industrial processes. Efforts are being made to dispose of PHDHs in a responsible manner, but some PHDHs have been accidentally released into the environment by industrial nations.

Due to their environmental persistence, PHDHs have become distributed in small quantities throughout the globe. The PHDHs have been transported from temperate regions to the arctic through the atmosphere and the marine food chain. In aquatic environments, PHDHs partition from water into organic material and then biomagnify up the food chain.

In Alaska, indigenous peoples that consume large quantities of subsistence foods from the sea are presumably exposed to these potentially toxic chemicals. The purpose of this chapter is to review what is known about the levels of PHDHs in subsistence foods in Alaska and the potential hazards PHDHs may pose to human health. A preliminary assessment of subsistence food safety is presented, and key knowledge gaps are identified.

Information about the concentrations of PHDHs in subsistence foods in Alaska is limited. In comparison to the monitoring programs that have been conducted in many other areas, PHDH data for Alaskan biota is minimal and scattered. The data that are available from several of the Alaskan studies are of limited utility due to poor or undeterminable analytical quality. It is important to consider the quality and limitations of existing PHDH data, because an uncritical interpretation of PHDH data can result in misleading conclusions. For the purposes of this review the quality of existing Alaskan data was scrutinized. While all available data were carefully considered, more weight was placed on PHDH data from studies that met rigorous standards of analytical quality.

To date, information about human exposure to PHDHs in Alaska is limited to the results of one recent study (Rubin et al. 1997). This collaborative study conducted by the U.S. Centers for Disease Control, the Alaska Native Health Board and the Alaska Area Native Health Service determined the levels of PCBs and other organochlorines in the serum of 126 Alaska Native women. The mean year of serum collection was 1985. At that time, the mean serum level of

PCBs was found to be 4.6 parts per billion (ppb), with 17.7 ppb being the highest individual value. This mean value of serum PCBs in Alaska Native women is at the low end of published values for human exposures in the United States, as mean serum levels throughout the country usually average between 4 and 8 ppb (ATSDR 1993).

There are a number of potential human health concerns related to PHDH exposure. Some consequences of acute, accidental high-dose PHDH exposure are obvious; the skin disorder chloracne is particularly diagnostic. Doses of PHDHs that cause such obvious effects are several orders of magnitude greater than the background PHDH exposures encountered by Alaskans through the food chain. Therefore, the risks about which we are most concerned when considering subsistence food issues in Alaska are chronic, long-term or subtle effects that may occur at very low PHDH dose levels. In particular, cancer, immunotoxicity, reproductive toxicity, and developmental/neurobehavioral toxicity have been considered as potential endpoints of PHDH exposure. Due to the controversy and confusion surrounding these endpoints and their relationships with PHDH exposure, this report considers these issues in some detail.

Thousands of studies have examined the potential health effects of PHDHs, and the results of these studies have often been conflicting and difficult to interpret. Overall, we conclude that there is some small element of risk of subtle health effects related to low-level PHDH exposure that may be exceedingly difficult to detect. It is also possible that there may be no adverse effects that result from low-level PHDH exposures such as those encountered through subsistence food consumption.

The potential risks associated with PHDH exposure through subsistence food consumption are smaller than the risks associated with a decreased reliance on traditional foods, or the risks associated with many other aspects of Alaskan life. A decreased reliance on traditional foods would have a negative net effect on human health in native Alaskan communities. Traditional foods have important nutritional benefits, as well as cultural and economic benefits. The Division of Public Health strongly encourages the continued consumption of traditional foods.

Levels of PHDHs vary substantially among species and tissues. The highest concentrations of PHDHs are likely to be found in the fatty tissues of animals that occupy the highest trophic levels of the marine food chain. In marine mammals, tissue levels are often higher in older animals, and in male animals relative to female animals. The limited data available suggest that PHDH levels in Alaskan inland fish are very low, and these fish can be consumed safely in unlimited quantities. Most Alaskan fish and seafood appear to have lower PHDH concentrations than fish from the Lower 48, which reflects the relatively pristine environment of Alaska. The highest current levels of PHDHs known in Alaska are in the blubber of stellar sea lions. Levels of PHDHs in beluga whale blubber from Alaska are somewhat higher than the levels found in Great Lakes fish, although they are within the same order of magnitude.

Future research should focus on addressing the following key knowledge gaps:

- Monitoring of subsistence species for PHDH levels in tissues should focus on six species: the beluga whale, pacific walrus, stellar sea lion, northern fur seal, ringed seal and bearded seal. Among Alaskan subsistence foods, the first four species have the potential to accumulate the greatest levels of PHDHs in their tissues, while the ringed seal is significant due to its moderate level of contamination and high rate of consumption by Alaskan natives. Monitoring the bearded seal is important because it is a preferred native food source, and very few samples have been analyzed for PHDH concentrations to date.

- Monitoring of PHDH levels in human tissues such as serum, adipose tissue or breast milk has only recently taken place in Alaska, and more information is needed. As the most direct indicator of human exposure to PHDHs, this information is essential in order for health officials to estimate the risks associated with the consumption of traditional foods. Measurement of PHDH levels in Alaskans will enable a comparison of their exposures and risks relative to people in other circumpolar areas that have previously been characterized, such as the Inuit of Quebec.

- The nature of PHDH exposure through the Alaska marine food chain needs to be characterized by use of sophisticated analytical methods that have not yet been used for Alaska samples. Patterns of PHDH congeners vary significantly among species as a function of trophic

level and metabolic capacity and among geographic areas, and these patterns influence toxicity. Congener-specific PHDH profiles which include the bioactive coplanar PCBs, PCDDs and PCDFs are needed for human tissues and for the more contaminated subsistence food species. In order to achieve adequate detection of important trace congeners, these coplanar analyses should focus on fatty tissues such as marine mammal blubber and human milk.

Polychlorinated Biphenyls (PCBs)

General Background Information on Polyhalogenated Diaromatic Hydrocarbons (PHDHs)

Polyhalogenated diaromatic hydrocarbons (PHDHs) are a group of structurally similar chemicals that include polychlorinated biphenyls (PCBs), dibenzo-*p*-dioxins ("dioxins") and dibenzofurans ("furans") (Figure 1). Complex mixtures of these chemicals are present as trace environmental contaminants in water, soil, sediment, air and biota throughout the world. Structural features common to all PHDHs include two aromatic rings and some degree of halogen substitution, and within each class of PHDHs the basic carbon structure is the same. Congeners within each class differ by the degree and position(s) of halogen substitution, most commonly by chlorine or bromine. There are 209 PCB congeners, 75 dibenzo-*p*-dioxin congeners, and 135 dibenzofuran congeners theoretically possible, although they are not all present in the environment.

Thousands of tons of PCBs were manufactured in many countries throughout

the Northern hemisphere from the late 1920s through the early 1970s for a variety of commercial purposes (Kimbrough 1980). PCBs are useful as heat transfer fluids, dielectric fluids for transformers and capacitors, plasticizers, hydraulic lubricants, flame retardants, and adhesives, in addition to a variety of other applications (Safe 1994b). Commercial PCB mixtures were usually marketed according to their percentage of chlorine content by weight. In the United States, the Monsanto Chemical Company manufactured PCBs under the trade name Aroclor. Products included Aroclors 1016, 1221, 1232, 1242, 1248, 1254 and 1260, where the last two digits denoted the percentage of chlorine content. Commercial PCBs were also produced by other companies in other countries under different trade names, including Clophen (Germany) and Kanechlor (Japan) (Safe 1994b). The United States explicitly banned the production and use of PCBs in the Toxic Substances Control Act of 1976 (Silbergeld et al. 1994), although the compounds are still present in older equipment manufactured before that time. In many other countries, including most members of the Organization for Economic Cooperation and Development (OECD), PCBs have also been banned or their uses restricted in commerce and industry (Silbergeld et al. 1994).

In contrast to the PCBs, dioxins and furans have not been intentionally manufactured. Rather, they are created as unintentional byproducts during the manufacture of other chemicals or as a result of some industrial processes. Trace levels of these chemicals are formed by the pulp and paper industry when pulp is bleached with chlorine (Hrutfiord et al. 1992), and during certain types of metal processing (Oehme et al. 1989). Spent graphite electrodes used in the chloralkali industry can be important localized sources of polychlorinated dibenzofurans (Zook et al. 1994). Chlorinated dioxins and furans are produced as unwanted byproducts during the manufacture of chemicals such as the wood preservative pentachlorophenol and certain herbicides that include 2,4-D and 2,4,5-T (Webster et al. 1994). Chlorinated dioxins and furans can be formed during the combustion of virtually any organic material when chlorine is present, and their production has been associated with the burning of coal and the incineration of wastes. Chlorinated dioxins and furans are also created by natural processes, both by microorganisms and as a byproduct of combustion (for example, from forest fires) (Gribble 1994). Forest and brush fires may be major sources of chlorinated dioxins and furans in the environment (Nestrick et al. 1982; Sheffield 1985), although there is considerable evidence that anthropogenic inputs may be more significant than these natural sources (Tong et al. 1990; Kjeller et al. 1991; Webster et al. 1994). Because dioxins and furans were never intentionally manufactured, efforts to reduce their creation have not focused on "banning" their production. Instead, regulations have focused on source abatement. Source abatement involves the alteration of production methods in problem industries to reduce dioxin and furan formation, as well as improved cleanup prior to the release of water or air from industrial processes into the environment.

PHDHs are an environmental problem because they are persistent and lipophilic. Because of their stability and resistance to biodegradation, many congeners undergo cycling and transport within the various compartments of the global ecosystem (Safe 1994b). Within aquatic systems, these

chemicals partition from the water to organic material and tend to bioaccumulate in fatty tissues. The combined properties of stability and lipophilicity result in the tendency of PHDHs to biomagnify in higher trophic levels of food chains (Muir et al. 1992c).

Factors unique to arctic ecosystems may enhance the deposition of organochlorines from the atmosphere and increase their environmental persistence. Polar regions may act as "cold traps" for some of the more volatile organochlorine compounds. Volatile, lower-chlorinated PCBs can be transported by the atmosphere from industrial nations in temperate regions to the arctic, where cold temperatures cause them to "distill" and settle (Wania et al. 1993). The more highly chlorinated PCBs are less volatile and are less likely to remain in the atmosphere to reach the arctic, but they may still arrive to the arctic in the bodies of migrating wildlife.

Distributions of PCB congeners in Canadian arctic fish and marine mammals appear to be regulated by trophic level bio-magnification properties, as they do not reflect the different physical-chemical properties (such as volatility) of individual congeners (Muir et al. 1988). Animals at lower trophic levels (such as arctic cod) contain patterns of PCBs similar to commercial PCB mixtures. At higher trophic levels (such as marine mammals), lower chlorinated PCB congeners are not detectable, and more highly chlorinated congeners are dominant in PCB patterns (Muir et al. 1988). This may be due to the ability of some marine mammal species to metabolize the lower chlorinated PCB congeners.

Outside of biological systems, persistence of PHDHs should be enhanced in the arctic environment due to slower reaction rates at low temperatures, reduced photolysis due to a low sun angle, and decreased biological activity (such as reduced scavenging of chemicals sorbed to sediments) relative to that of temperate climates (Wania et al. 1993).

In Alaska, the highest concentrations of PHDHs have been found in the fatty tissues of animals that occupy the highest trophic levels of aquatic food chains. In particular, PHDHs accumulate in the blubber and fatty tissues of marine mammals near the top of the marine food chain, such as beluga whales (Muir et al. 1992c). In fish, PHDH levels are higher in species that consume other fish, and in fatty species rather than species with lean meat. In fish these contaminants accumulate in the body over time, so that levels are usually higher in older, larger fish. The same often holds true for male marine mammals (Norstrom et al. 1994). However, adult female marine mammals have the ability to transport PHDHs to the fetus and to excrete PHDH contaminants in their breast milk, so that it is possible for their PHDH body burden to decrease following the birth and nursing of young. Therefore, in adult marine mammals males often have higher blubber PHDH concentrations than do females (Tanabe et al. 1987; Muir et al. 1992a).

Chemical Analysis of PHDH concentrations in environmental samples

Methodologies for analysis of PHDHs in environmental samples are continually being developed and improved upon. Different methods are used in various laboratories to isolate or "extract" PCBs from an environmental sample, and then to separate and quantify them. Data produced by

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different analytical methods may not be directly comparable, and it is essential to consider the quality of quantitative chemical analyses prior to their use in risk assessment.

A gas chromatograph is usually used to separate the individual PCB congeners, which are detected with either electron capture or mass spectroscopy. Many early analyses (pre-1980s) utilized low-resolution packed column chromatography to separate the congeners, which produced a relatively small number (5-12) of poorly resolved peaks. This method has largely fallen out of favor. Many of these older analyses are of marginal utility today, as PCB peaks were poorly resolved and often erroneously included non-PCB compounds such as toxaphene congeners, chlordanes and DDT-related chemicals.

Modern methods of chemical separation utilize higher resolution capillary columns that more adequately resolve most PCB congeners. With capillary column chromatography, 80-90 organochlorine peaks can be resolved from typical environmental extracts, and toxaphenes, chlordanes and DDTs can be distinguished from PCBs.

Following chemical separation, different methods can be used to quantify PCBs in a chromatogram. "Total PCBs" can be calculated by matching the pattern of PCB peaks from a sample with the pattern produced by commercial Aroclor mixtures, with use of pattern recognition algorithms such as COMSTAR (Burkhard 1987). The pattern of PCB peaks is matched with use of multiple regression procedures, and quantitation is performed by comparison to Aroclor response factors. While this method provides a good approximation of "total PCBs", it is not ideal because the

congener mixtures that are present in the environment are not the same as the commercial mixtures that were originally released.

Some congeners are more persistent than are others, so that their relative abundance increases in the environment over time (McFarland et al. 1989; Safe 1994b). Due to this difficulty, the most modern analytical approaches involve the quantitation and summing of targeted individual PCB congeners in the mixture. This approach tends to lead to smaller PCB concentrations than the "total PCB" approach (Giesy et al. 1997). All PCB congeners may not be included in the summation process. This is partly due to the fact that some congeners do not separate well on the gas chromatograph (Niimi et al. 1996).

Detection limits and large differences in the abundance of individual congeners can also present analytical challenges. A particular dilution of environmental extract may contain some congeners below the limit of detection, while other congeners are so abundant that their concentrations exceed the linear range of quantitation. Summed congener data may not be directly comparable from laboratory to laboratory, particularly if the same congeners are not chosen for quantitation, the same analytical standards are not utilized, or if procedures for data analysis and interpretation are different.

In all of the procedures discussed so far, the most toxic congeners (i.e., the flat or "coplanar" congeners) are generally not included in the analysis. While coplanar congeners are usually only present in small quantities in the mixture, because of their potency they can often contribute the vast majority of the overall toxicity of the

mixture (Johansen et al. 1994). Coplanar PCBs are an important component of overall PHDH toxicity in marine ecosystems, and the bioaccumulation of coplanar PCB congeners in carnivorous marine mammals is of particular concern (Kannan et al. 1989). A special extraction procedure and sophisticated instrumental analysis are required for coplanar PCB analysis. Coplanar analysis has not been performed for Alaskan environmental samples, a deficiency that should be corrected in the future.

Quality assurance and control (QA/QC) are essential aspects of PCB analysis. Without good QA/QC, there can be little confidence in the analytical data that are generated during PCB analysis. During the process of PCB extraction, trace quantities of these chemicals are isolated and concentrated from samples. Background PCB contamination in the laboratory can therefore be a serious problem, and blank samples must be periodically analyzed in order to assure that such contamination does not exist. Care must be taken to ensure that samples are not contaminated during the sampling process, during storage or during analysis. It is also important to analyze some samples more than once, to determine analytical precision or "repeatability". Another effective QA/QC procedure is to "spike" a subsample with a known quantity of a PCB congener, and then determine how much of that spike is recovered and quantitated during the analytical process.

The accuracy and precision of analytical measurements vary as the concentration of the analyte in the sample changes. Accuracy refers to the ability to quantify the concentration of an analyte correctly, while precision refers to the ability to obtain the same value when analyses are repeated

(regardless of whether that measurement was "accurate"). Each analytical method has a limit of detection for each analyte, below which the detected concentration is not significantly different from zero. Analytical methods also have a range of analyte concentrations for which accuracy and precision are optimized. As the concentration of an analyte diminishes and approaches the method detection limit, accuracy and precision of analytical results are decreased. In the optimal concentration range for an analyte the accuracy of a measurement should be ± 20%, but (by definition) near the limit of detection a detected concentration approaches an error of ±200% (Taylor 1989b). Since PHDH analyses often involve trace quantities of analyte, it is important to investigate and report limits of detection and the relative confidence of values in different data ranges.

It is desirable to obtain a sufficient quantity of sample in order to achieve analyte concentrations within the optimal analytical range whenever possible. This allows the collection of robust analytical data rather than a host of "non-detects". In order to accurately determine the concentration of trace PHDH levels in biota, it is often necessary to analyze fatty tissues that are most likely to contain the highest concentrations of these chemicals.

Rather than analyzing tissues that do not accumulate PHDHs to a significant extent (such as plants), limited resources would be more effectively utilized by increasing the sample size for animal species of concern. In marine mammals, PHDH levels are much higher in blubber than in internal organs, making their quantitation more robust. In humans, adipose tissue and breast milk are

two fatty tissues that are likely to contain higher PHDH levels. Unfortunately, the lipid content is low in human newborn cord blood, making PHDH quantitation difficult in this tissue.

Instrument detection limits are related to the concentration of analyte in a final extract. Consequently, detection of analyte in a sample can be enhanced by extracting a larger amount of sample in order to obtain more analyte molecules, and/or by reducing the final extract to a smaller volume. Pilot studies can be helpful to determine the sufficiency of proposed sample quantities.

Due to the varied methodologies that are used to quantitate PCBs in environmental samples, caution must be taken when interpreting values. In particular, it can be difficult to compare the results obtained by different laboratories, especially when the analyses were performed during significantly different time periods. Small differences in PCB quantities reported in various samples from different studies may not be meaningful, as they may represent measurement variability rather than inherent differences between samples. It is imperative that analytical methodologies be reviewed in detail, including the quality assurance and control programs, in order to have confidence in the data and its interpretation. Current efforts are emphasizing the certification of standard reference materials (Schantz et al. 1995), collaboration among arctic analytical laboratories, and rigorous analytical methodology and QA/QC protocols so that results can be more directly comparable (Becker et al. 1993b; Becker et al. 1997b).

Concentrations of PCBs in Subsistence Foods in Alaska

While some studies have been performed to determine the quantity of PCBs in subsistence foods in Alaska, the data are minimal and scattered. Far more comprehensive studies have been performed in the Canadian arctic (Murray 1992; Murray et al. 1993; Murray et al. 1994; Kuhnlein et al. 1995b; Murray et al. 1996; Jensen et al. 1997). Despite the relative paucity of data from Alaska, we may at least compare the available Alaskan data to the Canadian data in order to see whether they are in the same general range. While small differences in numbers may not be meaningful, as discussed above, it is probably quite safe to compare relative orders of magnitude between Canadian and Alaskan studies. In fact, some of the Alaskan samples have been analyzed in Canadian laboratories and the data are directly comparable.

We conducted an exhaustive review of the literature to investigate PCB concentrations in Alaskan fish and marine mammals. Peer-reviewed publications, government documents and accessible unpublished research reports were consulted. The quality of data from each study was carefully evaluated by examining the analytical methodology, methods and limits of quantitation, and quality assurance provisions. Although all data available were carefully considered, some data were not chosen for inclusion in this report because of their questionable quality. Problems with some studies included a lack of information about quality assurance or analytical methodology, outdated methodology and/or unacceptably high limits of detection for PCBs (McFall et al. 1986; Taylor et al. 1989; Miles et al. 1992).

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Selected PCB data for marine mammals and freshwater fish from Alaska and Canada that were obtained with use of similar analytical methods and quality assurance provisions are summarized in Tables 1 and 2 respectively. In the selected studies, high resolution chromatography was used to separate individual PCB congeners which were then summed to estimate total PCBs. Coplanar PCBs, dioxins and furans have not been measured in Alaskan samples. The data from Table 1 were used in a subsequent risk assessment presented later in this report.

The concentrations of PCBs presented in this report were determined from freshly caught animals prior to preparation for human consumption. Preparation methods can significantly reduce the concentration of PCBs in fish, particularly if fat and skin are removed or if the fish is cooked (USEPA 1996). PCB content was reduced by an average of 30% when Great Lakes fish were cooked (USEPA 1996). When fish are smoked their organochlorine contaminant burden can also be significantly reduced. In one study, PCB levels were decreased by 46% in Great Lakes Lake Trout that were smoked (skin-on) (USEPA 1996).

The effect that traditional food preparation methods unique to Alaskan Natives may have on PHDH concentrations has not been directly investigated. In a study of Canadian Inuit food preparation methods, the boiling of marine mammal blubber appeared to cause a modest decrease in PCB concentrations (Chan et al. 1996). In contrast, the omega-3 fatty acid content of walrus blubber was not changed by boiling or frying compared to raw blubber. Future studies should investigate how traditional methods of subsistence food preparation affect the levels of PHDHs in fish and

marine mammals as they are consumed by Native Alaskans.

Potential Health Effects of PHDHs

There are a number of public health concerns related to PHDH exposure. Biological changes following PHDH exposure can be measured using a variety of different endpoints. Some biochemical changes, such as the induction of certain enzymes, are quite specific to this class of compounds. However, the functional significance of such alterations is often not clear. Other potential endpoints that are functionally more relevant, such as cancer or immunosuppression, can be caused or influenced by a variety of factors and are more difficult to attribute directly to low-level PHDH exposures.

Some of the adverse biological effects that are associated with PHDH exposure have been observed primarily in laboratory animals treated with relatively high doses of PHDHs. It is difficult, and in some cases not valid, to extrapolate results obtained from high dose animal laboratory studies to the possible effects that might occur in humans exposed to chronic low doses. "Chronic" effects such as cancer that are observed in animal studies at high doses may be related to frank cellular toxicity and resultant cell proliferation, whereas the subtle long-term effects of low doses may be related to a complex alteration of hormonal systems involved in cell proliferation and differentiation. There is a large degree of variability in susceptibility to PHDHs among species, and there can also be great interindividual variability in susceptibility within a species (DeVito et al. 1995).

The most toxic PHDH congeners exert their effects on organisms through a common mechanism (Poland et al. 1982). In the cell, these PHDHs bind to the aromatic hydrocarbon receptor (AhR) (Landers et al. 1991), and the PHDH/AhR complex interacts with DNA. This interaction results in an alteration of gene expression, which mediates the responses of the organism to PHDHs (Landers et al. 1991). The toxicity of individual congeners is determined by their relative affinities for the AhR. Congeners that can assume a coplanar configuration have a greater affinity for the AhR, and are thus the more toxic PHDHs. Relatively few congeners are coplanar, and they are usually minor components of PHDH mixtures in the environment.

It is common to compare the AhR-mediated potency of individual coplanar PCB congeners relative to the potency of the most toxic congener, which is 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). The potency of each coplanar PCB congener can be expressed in terms of a "TCDD equivalency factor" (TEF). For example, a PCB congener that is half as potent as TCDD would have a TEF of 0.5. If congener-specific data are available, the overall toxicity of a mixture can be estimated by multiplying the concentration of each congener by its TEF and then summing the toxicities to calculate TCDD-equivalents (TEQs). This approach assumes that the toxicities of the congeners are additive, and that the congeners do not interact in an antagonistic or synergistic manner. The non-planar PCB congeners or their metabolites elicit some toxic responses, such as neurobehavioural, neurochemical, carcinogenic and endo-crinological changes, that do not appear to be mediated by the AhR (Ahlborg et al.

1992). The TEQ approach cannot presently be applied to these non-AhR responses.

The degree of hazard associated with human exposure to PHDHs is controversial, and scientific opinions have changed over time (Hanson 1991). In early assessments, TCDD was dubbed "the most toxic synthetic chemical known to man". This was largely due to its great potency in guinea pigs, which die following exposure to minute concentrations of TCDD (the LD50 is approximately 0.6 μg/kg for this species).

With further study, it became apparent that there are dramatic differences in species sensitivity to TCDD. For example, about a 1,000 to 10,000-fold greater dose of TCDD is required to kill a hamster than a guinea pig (DeVito et al. 1994). On the comparative scale of species sensitivity, some scientists think that humans are relatively insensitive to the negative effects of TCDD and other planar PHDHs.

Following several large accidental exposure incidences, the only observed adverse effects in humans which have been unequivocally linked to PHDHs have been chloracne (Suskind 1985) and other skin disorders (Lu et al. 1985), although there may also be an association with increased cancer incidence in heavily exposed populations (Bertazzi et al. 1987; Fingerhut et al. 1991; Bertazzi et al. 1993). Following an industrial accident in Seveso, Italy at which TCDD was released, animal mortality was about 25% in the most directly impacted zone although none of the 733 persons present in the zone were killed (Pocchiari et al. 1979; Bertazzi et al. 1994). However, current analyses are challenging the view that humans are insensitive to the

toxic effects of PHDHs (DeVito et al. 1995). There is concern that exposure to chronic, low levels of PHDHs may produce subtle toxic effects that are difficult to detect.

The accidents which produced obvious deleterious effects in humans involved exposures to PHDHs that were orders of magnitude greater than the background exposures in the United States, or the exposures related to the consumption of traditional foods in the arctic. For example, adverse birth outcomes such as decreased birth weights, delayed developmental milestones and skin disorders occurred in the offspring of Taiwanese women who consumed rice oil contaminated with PHDHs. The average body burden of the women involved in that poisoning incident known as Yu-Cheng was 2130 ng TEQ/kg body weight, which was 164 times greater than the average human background body burden of 13 ng TEQ/kg body weight (DeVito et al. 1995).

The risks about which we are most concerned when considering subsistence food issues in Alaska are chronic, long-term or subtle effects that may occur at very low dose levels. The following evaluation will discuss four possible chronic effects that are of primary concern with regard to PHDH exposure: cancer, neurobehavioral changes, reproductive impairment and immuno-suppression. In general, these negative health outcomes can all be caused or influenced by a variety of factors and are difficult to attribute directly to low-level PHDH exposure in humans.

Cancer

Cancers are diseases characterized by the abnormal proliferation of cells, and they occur in all human populations. The incidence of cancer increases greatly with age. In the United States, cancer is second only to heart disease as a cause of death and accounts for 22% of all deaths (Fraumeni et al. 1993). Only a small proportion of these cancers are related to exposure to hazardous chemicals from the workplace or environment (Ames et al. 1995). Cancers have increased greatly in Americans in the past 40 years, due mostly to a large increase in life expectancy and to the high incidence of cigarette smoking since the 1940s. In the United States, smoking accounts for about 40% of all cancer deaths in men and about 20% of all cancer deaths in women (Fraumeni et al. 1993).

PCBs have been classified by the USEPA as probable human carcinogens. The more highly chlorinated PCB mixtures cause liver cancer in rodents, probably through a promotion mechanism (Safe 1989). The increased incidence of liver cancer in rodents usually occurs at high doses that are toxic to liver cells (Kociba et al. 1978; Tatematsu et al. 1979). The most toxic PHDH congener, TCDD, acts as a tumor promoter in laboratory animals (Pitot et al. 1980) but has weak or no initiation activity (Shu et al. 1987).

Tumor promotion appears to be mediated by the Ah receptor, and likely results from modifications in hormonal systems involved in cell growth and differentiation such as the epidermal growth factor and estrogen receptor. Coplanar PCBs with dioxin-like activity may act through a similar Ah-mediated tumor promotion mechanism. The doses of PHDHs that were required to induce cancer in experimental animals were large, and involved an estimated body burden (in terms of ng TEQ/kg body weight) that was 100 to 10,000 times higher

than the background body burdens of TEQs found in humans today (DeVito et al. 1995). A recent analysis has convincingly shown that humans are significantly less susceptible than rats to TCDD-induced carcinogenesis, and that low-level background exposures to TCDD are not associated with an increased cancer risk in humans (Aylward et al. 1996).

PHDHs can indirectly modulate the incidence of cancer caused by other chemicals. The induction of phase I and phase II drug-metabolizing enzymes can lead to either an increase or a decrease in the toxicity of a variety of chemicals. In some cases, potent carcinogens are metabolized and cleared from the body more rapidly following PHDH-induced enzyme induction, or adduct formation is otherwise reduced, such that PHDHs can be protective and act as anti-carcinogens. For example, aflatoxin B_1-induced hepatocellular carcinomas in trout can be inhibited by pre-initiation treatment with PCBs (Makura et al. 1974; Hendricks et al. 1977; Shelton et al. 1986). Exposure of women to high levels of TCDD has also been associated with a slight decrease in the incidence of estrogen-dependent cancers of the breast and uterus (Bertazzi et al. 1993), which could possibly be related to the antiestrogenic properties of TCDD (Safe et al. 1991).

A number of epidemiological studies have been performed to examine the incidence of cancer in human populations that have been accidentally exposed to high levels of PHDHs (Hardell et al. 1994). In general, it has been difficult to detect statistically significant differences in the incidence of relatively rare forms of cancer between PHDH-exposed and control populations, because very large numbers of study subjects are required to detect such changes.

For example, in a population of 4,824 people exposed to high levels of TCDD during a chemical plant explosion in Seveso, Italy (Zone B), six cases of hepatobiliary cancer were detected among those who had lived in the zone for at least five years (Bertazzi et al. 1993). This was a statistically significant increase in incidence from the 2.1 cases expected. Even following the extreme TCDD exposures experienced in Seveso, detecting a health impact was difficult because of the rarity of cancer incidence, the small number of exposed individuals, and the short length of follow-up.

Exposure to PHDHs has not been consistently associated with one particular form of cancer, but instead has been associated with different types of cancers in various studies. This observation confirms that if they cause human cancer, PHDHs are not directed towards one specific target organ but instead exert a pleiotropic response which affects the endogenous regulation of cell differentiation and proliferation. However, certain types of cancer are more commonly associated with PHDH exposure, including soft tissue sarcoma, cancers of the hematopoietic system, and cancers of the liver and extrahepatic biliary system.

In humans, high doses of PHDHs have been associated with cancer of the liver and extrahepatic biliary system, including the bile ducts and gall bladder (Brown 1987). Liver cancer has also been observed in experimental animals treated with high doses of TCDD (Kociba et al. 1978). However, PHDHs are considered to be a minor risk factor for hepatocellular carcinoma (HCC) in comparison to other known causes. It is estimated that approximately 75% of HCC cases

worldwide can be attributed to one of three causes: hepatitis B virus, alcohol, or aflatoxin (a natural product of mold that can contaminate foods) (Falk 1982). Cancers of the biliary tract are usually associated with the incidence of gall stones, although hormonal, nutritional and genetic factors are also important (Fraumeni et al. 1982).

Information available to date does not support the existence of a causative relationship between PHDH exposure and cancer incidence among Alaska Natives. In a recent study, no relationship was observed between the incidence of breast cancer and serum levels of PCBs or other organochlorine chemicals among Alaska Native women (Rubin et al. 1997). However, it is important to note that this study had limited power to detect such a relationship due to its relatively small sample size, and additional research is needed. Limited data suggest that liver and gall bladder cancer rates may be elevated among Alaskan natives compared to the overall white population of the United States (Nutting et al. 1993). It is unlikely that PHDHs are involved in the etiology of these diseases, because exposures of Alaskan natives to PHDHs are much lower than those experienced by accidentally exposed human populations in which carcinogenic effects have been observed. The higher rate of liver cancer in Alaska Natives relative to the total U.S. population has been related to a greater prevalence of hepatitis B infection among Alaskan Natives (Lanier et al. 1989).

Immunotoxicity

The immune system may be the most sensitive target for PHDH toxicity in experimental animals. The evidence for clinically relevant immunotoxicity in PHDH-exposed humans is less consistent

(DeVito et al. 1995). However, there is concern that low levels of PHDHs may have subtle immunosuppressive effects in exposed humans, making them less able to avoid or combat infectious diseases or cancer. Alternatively, an enhanced immune response could have negative repercussions such an increased incidence of allergic reactions or autoimmune diseases. The immune system involves a complex interaction of many cell types and soluble mediators, and immune responses are time-dependent relative to antigen exposure. Immunotoxicological assessments must consider these levels of complexity in order to produce interpretable results. A wide variety of immunological endpoints have been studied with regard to the toxicity of PHDHs.

Immunosuppressive effects of PHDHs are largely modulated through the Ah receptor (Silkworth et al. 1982; Kerkvliet 1994). The immunotoxicity of PHDH mixtures are often not additive, as certain PCBs antagonize the immunotoxic effects of other PHDHs including those of TCDD (Harper et al. 1995). Therefore, the TEQ approach can not be accurately used to estimate the immunotoxic potency of PHDH mixtures at this time (Tryphonas 1994).

Immunotoxic effects have been observed in marine mammals fed fish from contaminated areas. In a 2.5 year feeding study, captive harbor seals fed fish from the heavily polluted Baltic Sea exhibited an impairment of T cell mediated immune responses (De Swart et al. 1995) and a suppression of natural killer cell activity (Ross et al. 1996) in comparison to seals fed fish from the relatively uncontaminated Atlantic Ocean. Natural killer cells are an important first line of defense against viral infections (Golub et al. 1991). Consumption of

dioxin-like PHDHs was about ten times higher in the Baltic herring-fed than in the Atlantic herring-fed seals (288 ng TEQ and 29 ng TEQ per day respectively) (Swart et al. 1994), and total TEQs in the blubber of test subjects following two years on the different diets were approximately 3.4 times greater in the Baltic- than Atlantic-fed seals (Ross et al. 1996). Although these chemicals might have contributed to the immunosuppression observed, it is possible that other immunosuppressive agents may have been present in the fish as well.

Consumption of Baltic Sea fish may also affect the human immune system, since reduced numbers of natural killer cells were found in the blood of 23 adult males with high fish consumption relative to a group of 20 men who did not eat fish (Svensson et al. 1994). Differences in natural killer cell numbers were small, however, and all other immune system parameters measured were not significantly different between the two groups. A number of constituents that can impair the activity of natural killer cells were present in the fish and were highly intercorrelated, including methyl mercury, PHDHs, p,p'-DDT, and omega-3 polyunsaturated fatty acids. Therefore, the specific causative agent of natural killer cell impairment could not be identified. Furthermore, the observed differences were not likely to have functional significance. It should be emphasized that concentrations of PHDHs are much lower in Alaskan fish than in fish from the highly contaminated Baltic Sea. In one study, concentrations of PCBs and DDTs were ten times lower in cod from the Western Tana Fjord (Barents Sea) than in cod from the Gulf of Finland (Baltic Sea) (Vuorinen et al. 1989).

There is some concern that contaminant-induced immunosuppression may have contributed to a number of epizootics in recent years among seals and dolphins inhabiting polluted coastal waters (Sarokin et al. 1992; Aguilar et al. 1994). In mice, enhanced susceptibility to influenza virus was observed following a single dose of 10 ng TCDD/kg body weight, making viral host resistance the most sensitive adverse effect yet reported for TCDD in this species (Burleson et al. 1996). In Europe, a large number of marine mammals died from infections with morbillivirus, and it is hypothesized that environmental contaminants may have rendered the stricken animals less immunocompetent to fight the disease (Hall et al. 1992). If such trends were global in nature, a decrease in marine mammal populations due to reduced immunocompetence could negatively affect Alaskan natives by reducing their traditional food supply. Fortunately, Alaskan marine mammals are not exposed to the same degree of contamination as are marine mammals from industrial coastal areas. For example, PCBs in common seals from the North and Baltic Seas were 34 times higher than PCBs in ringed seals from the arctic island of Spitzbergen (Luckas et al. 1990). Large-scale marine mammal epizootics such as those described in Europe and the east coast of the continental U.S. have not been observed in Alaska.

Different approaches have been used to study immunological endpoints of PHDH exposure in humans. Endpoints such as the incidence of infections and the response to vaccinations are integrated measurements of immune function that are highly relevant to human health, but they are non-specific to PHDH exposures. The number and relative quantities of various subsets of immune-related cells (lymphocytes) can function as specific markers of immune function, and they are often quantified in the blood.

Immune cells from PHDH-exposed humans can be cultured, and their proliferative response to challenge with specific mitogens or antigens can be assessed. Investigations of the *in vitro* function of immune cells in culture can diagnose specific aspects of the immune system, but are more difficult to relate to *in vivo* relevance.

Most immunological parameters have a very broad range of normal values, and small differences are often not biologically meaningful (Kerkvliet 1994). Many of the *in vitro* assays that have been performed with immune cells from PHDH-exposed humans have produced conflicting results in different studies. There are at least two possible reasons for this. First, *in vitro* assays can be greatly influenced by laboratory procedures and culture conditions. For example, when 23 commercial lots of serum were tested as components of cell culture media for *in vitro* assays, five of the serum lots supported a suppression of T-dependent humoral immune response while the remaining lots demonstrated an apparent protective effect against the TCDD exposure (Morris et al. 1991). Second, *in vitro* studies remove the complex influence of non-lymphoid factors on immune function, such as circulating endocrine hormones. Endocrine hormones such as glucocorticoids, sex steroids, thyroxine, growth hormone and prolactin are involved in the regulation of the immune response, and many of these hormones are influenced by PHDHs (Kerkvliet 1994). The *in vivo* response to an antigen challenge such as sheep red blood cells (SRBD) can also be measured. One advantage of this approach is that it integrates the interactions of many immune systems components as well as non-lymphoid factors such as the endocrine system.

Epidemiological investigations of immunological characteristics have been performed in several human populations that were accidentally exposed to PHDHs. The epidemiological studies were often hampered by small sample sizes, and actual exposures to PHDHs were often not measured. The studies were conducted at very different times post-exposure, and in some cases several decades had elapsed between the time of exposure and the time of evaluation. This could be a problem because immunological parameters could recover over time following an accidental exposure. Representative studies are presented in Table 4, which illustrates only a fraction of the wide variety of endpoints that have been measured and the inconsistency of the results obtained among various studies.

The incidence of infections has been related to PHDH exposures in several human populations. In Taiwanese Yu-Cheng patients "frequent" infections of the respiratory tract and skin were observed, although the incidence was not compared with a control group (Lu et al. 1985). Following the accidental release of large quantities of TCDD in Seveso, Italy, an increase in reports of infectious childhood diseases occurred, but it was thought to be due to increased reporting by doctors rather than to TCDD exposure per se (Pocchiari et al. 1979). In a population from the Netherlands with a relatively high background exposure to PHDHs, there was no significant correlation between pre- and post-natal PHDH exposure and the number of infections during the first 18 mo of life, or in vaccination effectiveness in the infants (Weisglas-Kuperus et al. 1995). Total TEQs in that Dutch population (Koopman-Esseboom et al. 1994a) were similar to

TEQs found in Inuit women from arctic Quebec (Dewailly et al. 1992; Dewailly et al. 1994) (61 and 67 ppt in breast milk fat, respectively as calculated in Figure 2).

The possibility of PHDH-induced immunosuppression among the Canadian Inuit has been proposed. The incidence of infectious diseases such as otitis (Julien et al. 1987) and meningitis (Proulx 1988) has been much greater in infant Inuit from northern Quebec than in infants from other populations, and there has been speculation that PHDHs in Inuit food might have been responsible via immunosuppressive mechanisms (Dewailly et al. 1989; Dewailly et al. 1993). Given the lack of effect on immune function or infection incidence in the Dutch population with similar TEQ exposures, a significant role for PHDH-mediated immunosuppression in the Inuit is highly unlikely.

There are other known risk factors that are far more likely to be responsible for the high incidence of otitis media among the Inuit, such as low socioeconomic status, family history, house-crowding, or exposure to tobacco smoke (Julien et al. 1987; Infante-Rivard et al. 1993). Race may also be an important risk factor for otitis media. Historically, American Indians, Canadian Eskimos and Native Alaskans have experienced a much greater prevalence of otitis media than have white children, while black children seem to be at lesser risk than white children (Infante-Rivard et al. 1993). Also, breast feeding has been shown in many studies to be a significantly protective factor against the development of otitis media (Infante-Rivard et al. 1993), despite the fact that infants may be exposed to PHDHs in breast milk. There are potential confounding immunosuppressive influences within the fish diet itself, such that it would

be difficult to separate the influence of PHDHs. For example, the omega-3 polyunsaturated fatty acids found in fish are potent immunosuppressive agents (Kelley et al. 1993).

No clear pattern of PHDH-mediated immunotoxicity in humans has emerged from epidemiological studies (Table 3). Parameters such as the CD4/CD8 ratio, immunoglobulin levels and lymphocyte proliferation were decreased in PHDH-exposed individuals in some studies, but increased or unaffected in PHDH-exposed individuals in other studies. It is also important to recognize that the effects of chronic low-level exposures to PHDHs may be fundamentally different from those that occur following accidental high-dose exposures. In marmoset monkeys, the effect of repeated low exposures of TCDD on a T cell subpopulation (helper-inducer or "memory" cells) was the opposite of that which occurred at higher exposures (Neubert et al. 1992). Therefore, extrapolations from data obtained at high TCDD dose levels to much lower exposures are probably not justified with respect to immune system effects, and the "possible effects induced by high occupational exposures or in victims of accidents are not necessarily to be expected .... at the much lower exposures of the general population" (Neubert et al. 1992).

Reproductive and Developmental Toxicity; "Endocrine Disruption"

Human reproduction and fetal development are regulated by the endocrine system, and involve a complex interplay of hormonal signals that can produce their effects at minute doses. Xenobiotic chemicals (that is, chemicals originating from outside the body) can interfere with hormonal signals in

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a variety of ways. Some chemicals interact with hormone receptors. At times the chemical interacting with the receptor acts as an agonist, and mimics the hormone to "turn on" the receptor and induce biological effects. In other cases the chemical interacting with the receptor acts as a hormone antagonist. Effectively, it does not "turn on" the receptor but instead blocks the hormone from the receptor site, such that the hormone can not carry out its intended function (Klinge et al. 1992). Xenobiotics can also interfere with signals by altering the production, metabolism or clearance kinetics of hormones, or by influencing the regulation of hormone receptor levels.

It has long been recognized that exposure to some xenobiotic chemicals can interfere with hormonal signals and result in adverse consequences (Birnbaum 1994). Some plants found in nature produce chemicals that can cause sterility in livestock or wildlife consumers (Cheeke et al. 1985). Also, the drug diethylstilbestrol (DES) has produced vaginal cancer and other abnormalities of the reproductive organs in female offspring of mothers who took the drug during pregnancy (Herbst 1981). These adverse outcomes were not expressed until the daughters reached puberty. This drug is a potent mimic of the female hormone 17-β-estradiol, and it produced its negative effects by altering the delicate hormonal balance of sex hormones in the womb during the critical period for sexual differentiation and development. More recently, environmental contaminants have been implicated as the cause of severe developmental abnormalities of the reproductive system among hatchling alligators from a Florida lake, including abnormal gonadal morphology, abnormal sex steroid concentrations, elevated neonatal mortality, and significantly reduced phallus size in male juveniles (Guillette 1995).

The process of sexual differentiation is particularly sensitive to hormone alterations. The differentiation of sex organs from bipotential gonadal tissue occurs during early prenatal development and is determined by the milieu of sex hormones present during a critical period (Loomis 1986; Crews et al. 1995). In experimental animals, sexual differentiation of the brain and many aspects of adult sexual behavior are also determined by sex hormones present in the womb during finite critical periods of development. For example, early sex hormone administration can have profound permanent sex reversing effects on adult behavior in birds (Adkins-Regan 1987). When male Japanese quail embryos are injected with 1 μg estradiol or 500 μg testosterone during a critical period of incubation, they can be completely behaviorally sex reversed. As adults they fail to mount, crow, or strut; they are completely demasculinized and are behaviorally indistinguishable from females (Adkins 1979). This effect is due to a fundamental change in the neural substrate underlying behavior.

Recently there has been great concern that environmental contaminants, including PHDHs, may "disrupt" the endocrine system and cause deleterious reproductive and developmental effects in exposed wildlife and humans (Birnbaum 1994). Although much attention has been paid to the "estrogenic" activity of various xenobiotic chemicals (perhaps due to the model toxicity displayed by DES), this is an overly simplistic approach to the issue.

Chemicals may have estrogenic, anti-estrogenic, androgenic or anti-androgenic

activities, which can by different mechanisms each alter the effective hormonal milieu in the womb. TCDD and structurally related PHDHs displayed anti-estrogenic properties in human breast cancer cells (Krishnan et al. 1993). The complex mixture of estrogenic and anti-estrogenic chemicals humans are exposed to through the environment and diet may be contra-active, and result in an insignificant overall effect (Safe 1994a). A more holistic approach to the problem of PHDH-induced endocrine disruption recognizes the profound interdependence of hormones, other soluble factors and immune system parameters in the body. Through alterations in gene expression PHDHs can influence a wide variety of hormones and soluble regulatory factors and alter the communication between cells, possibly by influencing gap junctions (Trosko et al. 1981). They therefore have the ability to influence reproduction and development not only by mimicking or blocking sex hormone activity, but also by altering processes of cell differentiation and growth during critical periods.

It is necessary to consider several factors when evaluating the potential for xenobiotics to interfere with the endocrine system. The potency of the xenobiotic and the timing of the exposure at the relevant target cell or organ are both crucial. Many of the pesticides that have been termed "estrogenic" exhibit activity that is at least a thousand-fold weaker than endogenous estradiol, and very high doses of the pesticides were required to elicit observable estrogenic effects in experimental animals (Kupfer et al. 1980; Eroschenko 1981). The intake of environmental contaminant-related "estrogen equivalents" is minuscule in comparison to the quantity of "natural" estrogens produced by the body or

consumed in food, and it is highly unlikely that trace contaminants could contribute significantly to the body's estrogen balance (Safe 1995).

Another consideration is that the dramatic disruption of a process such as sexual differentiation can only happen during a very limited time period, which may only last a few days. The nature of the exposure can greatly influence the effect observed. Some hormones are only active when presented as pulses, while slow steady exposures are not active (Gangong 1985). Due to the complexity of the biological systems involved, information obtained from *in vitro* screening assays (for example, for estrogen receptor binding) should be interpreted with caution until the chemical in question has been confirmed to produce reproductive or developmental toxicity *in vivo* using realistic exposure concentrations and scenarios.

The PHDHs have exhibited reproductive and/or developmental toxicity in several animal models (Theobald et al. 1994). For example, in the rat a single maternal oral dose of TCDD on day 15 of gestation resulted in an impairment of several reproductive parameters in male offspring. Maternal doses as low as 0.16 μg TCDD/kg body weight produced significant dose-related delays in testicular descent, decreases in seminal vesicle and ventral prostate weights at several stages of sexual development (Mably et al. 1992c), and sexual behavior during adulthood was demasculinized in male offspring (Mably et al. 1992b). Decreases in epididymis and cauda epididymis weight, daily sperm production, and cauda epididymal sperm number were observed at the lowest maternal dose tested (0.064 μg TCDD/kg body weight) (Mably et al. 1992a). Despite

these alterations, reproductive outcomes of matings between the male offspring and control female rats were not significantly impaired during this study, even at the highest dose tested (1.0 μg TCDD/kg body weight) (Mably et al. 1992a).

Endpoints related to reproduction have been investigated in human males exposed to PHDHs. It has been reported that sperm counts have dramatically decreased in humans during the past 50 years throughout the world (Carlsen et al. 1992), and it was suggested that environmental contaminants might be to blame (Colborn et al. 1996). It has similarly been noted that testicular abnormalities have increased in recent decades, and might also have an environmental cause (Giwercman et al. 1993). Endocrine-modulating chemicals such as PHDHs are often implicated as possible culprits of male reproductive toxicity in the literature (Colborn et al. 1996). The evidence in support of PHDH-induced sperm count declines is, however, nonexistent. There is serious debate as to whether a decline in sperm count has even occurred (Bromwich et al. 1994; Lipshultz 1996). Sperm counts vary dramatically among geographic areas, and many of the differences originally detected were related to geographic location rather than to time (Fisch et al. 1996; Paulsen et al. 1996).

Several studies have investigated the effect of TCDD exposure on testosterone and gonadotropin levels in human serum. Testosterone levels were lower in industrial workers exposed to TCDD than in a reference population, while luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels were higher in the TCDD-exposed workers than in the reference population (Egeland et al. 1994). The hormone differences measured were of no biological significance, as the magnitude of the measured hormone differences was very small. Primary gonadal failure was not involved, because low testosterone and high LH and FSH were not observed in the same individuals. The workers in that study had rather high levels of TCDD in serum (63% had levels above 33.3 ppt). Testosterone and gonadotropins were measured in another group of TCDD-exposed males, the Ranch Hand veterans involved in herbicide application in Vietnam (Henriksen et al. 1996). In that cohort TCDD body burdens were lower (only 26% had TCDD levels above 33.3 ppt in serum), and no consistent or meaningful associations between TCDD and hormone levels were found. In a related study of the Ranch Hand veterans, an association between paternal dioxin levels and reproductive outcomes such as birth defects and developmental disabilities was not apparent (Wolfe et al. 1995).

One study involving chronic, low-level exposure of rhesus monkeys to TCDD provides information that is of considerable relevance to human risk assessment. Monkeys were divided into three groups of eight animals each, which received 0, 5 or 25 ppt TCDD in food for a period of four years. Following this treatment period, their reproductive capacity was assessed. Reproductive outcomes were compromised in the animals treated with 25 ppt TCDD (Bowman et al. 1989). Although five of eight females in that group conceived, only one gave birth to a viable infant. The most disturbing outcomes of this experiment were discovered ten years after termination of dioxin treatment, when an elevated and dose-related incidence of moderate to severe endometriosis was observed in monkeys from both dioxin treatment groups (Rier et al. 1993).

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Endometriosis is characterized by the growth and proliferation of endometrial cells at sites outside the uterus, and occurs exclusively in menstruating species. Both mild and severe forms are associated with infertility and chronic pain. These findings were particularly significant because the mode of exposure (chronic low levels in food) and species (non-human primate) were particularly relevant to human TCDD exposures. In addition, both the time-frame of toxicity and the endpoint measured were beyond the scope of traditional laboratory studies with rats. However, these results were from one study involving a small number of monkeys. Additional laboratory studies are needed to confirm those observations, and epidemiological studies are needed to investigate whether PHDH exposures may be associated with endometriosis in humans.

Reproductive outcomes in humans have been assessed for relationships with PHDH exposure. Exposure to PHDHs was often not adequately measured in study subjects in these epidemiological studies (Sweeney 1994). The possible relationship between fetal mortality and PHDH exposure has been examined in several studies. Many early resorptions occur prior to the clinical recognition of pregnancies, which makes it very difficult to quantify any early-stage mortality that might be associated with PHDH exposure.

The contamination of the Michigan food supply with polybrominated biphenyls in the mid-1970's did not have a detectable impact on the rate of late spontaneous abortions (after 20 weeks gestation) (Humble et al. 1984). In New York state, consumption of Lake Ontario fish that contained PCBs and other environmental contaminants was not associated with an increased risk of spontaneous fetal death (Mendola et al. 1995).

Birth size and gestational age have also been examined in relation to PHDH exposure, because decreased prenatal growth has been observed in animals treated with TCDD (Theobald et al. 1994). Small decreases in gestational age (6.6 days) were noted among female workers occupationally exposed to PCBs (Taylor et al. 1984). Birthweights were also reduced in infants born to the occupationally exposed women, but most of that reduction was explained by the decreased gestational age. An association between PCB exposure and decreased infant birth weight was also observed in a population of women who consumed large quantities of Lake Michigan fish (Fein et al. 1984), but the influence of other chemicals present in the fish could not be adequately determined due to the low resolution analytical methodology employed. In a population in North Carolina with background PCB exposure, there was no relationship observed between PCB levels in maternal milk fat at birth and infant birth weight (Rogan et al. 1986).

The effects of PHDHs on fetal and neonatal growth and development may be related to thyroid regulation (Feeley 1995), although the relationship between thyroid hormone levels and PHDH exposure has been inconsistent among studies of human infants (Pluim et al. 1993; Koopman-Esseboom et al. 1994b; Nagayama et al. 1996). Another endpoint of prenatal and neonatal exposure to PHDHs that has received a great deal of attention concerns cognitive and neuro-behavioral development, which will be discussed in the next section.

In conclusion, exposure of humans to high levels of PHDHs following industrial

accidents or severe poisoning incidents has resulted in some adverse reproductive outcomes. Skin discoloration and eye discharge were observed in infants born to women who consumed PHDH-contaminated rice oil during the Yusho and Yu-Cheng poisoning incidents (Hsu et al. 1994; Masuda 1994). Other adverse outcomes such as increased rates of spontaneous abortion, stillbirths and birth defects are less well documented, but may have occurred following these extreme exposures. On the other hand, low-level, background exposures such as those experienced in the arctic are not likely to present a significant risk to human reproductive outcomes. Epidemiological studies focused on fish-eaters or others with background PHDH exposures have not shown consistent results, and any effects observed have been very minor.

Neurotoxicity

PHDHs have caused a number of changes in the neurochemistry and neurobehavioral development of laboratory animals. Interestingly, it appears that many of the neurotoxicological effects of PCBs may not be regulated by interaction with the Ah receptor. In fact, many of the neurotoxicological effects have been attributed to the non-Ah active PCB congeners that have chlorine atoms at two or more ortho positions. While TCDD and coplanar congeners have been observed to effect the nervous system, the effects are qualitatively and quantitatively different from those caused by PCB mixtures (Seegal et al. 1994a). In this important respect, the neurotoxicity of PHDHs is quite different from other endpoints of toxicity that have been previously discussed.

Feeding studies with non-human primate adults have demonstrated that ortho-substituted PCB congeners can cross the blood-brain barrier and induce changes in the concentration and activity of the neurotransmitter dopamine in the brain (Seegal et al. 1991; Seegal et al. 1994b). The relationship between PCB exposure and dopamine concentrations is complex, and appears to be dependent upon the magnitude of the dose, the age at exposure, and perhaps the composition of the PHDH mixture. For example, adult nonhuman primates fed 3.2 mg Aroclor 1016/kg body weight daily for 20 weeks exhibited a decrease in brain dopamine (Seegal et al. 1994b), while female rats born to mothers fed 100 ppm Aroclor 1016 exhibited an increase in brain dopamine and other neurotransmitters (Seegal et al. 1994a).

Behavioral studies have been undertaken to determine the functional significance of PHDH-induced changes in the nervous system. In a series of experiments in which monkeys were exposed perinatally to either TCDD or PCBs, learning was impacted in both cases but in qualitatively different ways (Seegal et al. 1994a). Monkeys born to mothers fed 1.0 ppm Aroclor 1016 exhibited impaired spatial discrimination-reversal learning but facilitated object discrimination-reversal learning (Schantz et al. 1989b), while the exact opposite effect was observed in monkeys born to mothers fed 5 ppt TCDD (Schantz et al. 1989a; Bowman et al. 1990). In addition, monkeys born to mothers fed 2.5 ppm Aroclor 1248 exhibited impaired performance on delayed spatial alternation tests at 4 to 6 years of age, although they had not been exposed since they were weaned at 4 months of age (Levin et al. 1988). In contrast, these deficits were not seen in TCDD-exposed monkeys (Seegal et al. 1994a). Based on

the combined results of behavioral and neurochemical experiments, it has been hypothesized that PCBs may cause deficits in spatial learning and memory by altering dopamine input to the dorsolateral area of the prefrontal cortex (Seegal et al. 1994a). These alterations may not be mediated by the Ah receptor, and the mechanisms behind TCDD-induced neurotoxicity are less well understood.

Several large epidemiological studies have been undertaken in an attempt to determine what effect PHDH exposure may have on the neurological system of exposed humans. These efforts have largely focused on the neurological development and cognitive functioning of children exposed *in utero* to PHDHs. In the Yu-Cheng poisoning incident in Taiwan, children that received high doses of heat-degraded polychlorinated biphenyls and dibenzofurans *in utero* displayed a significant decrease in cognitive function when compared with matched controls (Chen et al. 1992). Yu-Cheng children scored approximately 5 points lower than controls on several standard intelligence tests, an effect that remained consistent during yearly tests from 2.5 to 7 years of age. In contrast to the Yu-Cheng study of a highly exposed population, several other neurodevelopment studies have focused on children exposed to lower, background concentrations of PHDHs.

In one series of studies, the maternal consumption of fish from Lake Michigan was found to be associated with impaired intellectual function in young children (Jacobson et al. 1985; Jacobson et al. 1990; Jacobson et al. 1992; Jacobson et al. 1996). This impairment was attributed to *in utero* exposure to PCBs from the fish. The maternal consumption of fish from Lake

Ontario was also associated with neonatal behavioral test deficits in offspring, although the causative agent in the fish was not identified (Lonky et al. 1995). In another study, the relationship between background PCB exposure and neuro-development was examined in children from North Carolina (Gladen et al. 1988; Rogan et al. 1991). Estimated prenatal exposures to PCBs were associated with decreased psychomotor scale scores at 6, 12, 18 and 24 months of age.

In both the Lake Michigan and North Carolina cohorts, neurological deficits were not associated with PHDH exposure from breast feeding. In contrast, in a large Dutch study prenatal exposure to PHDHs was not associated with neurological development, while post-natal exposure to PHDHs from breast feeding was associated with reduced neurological optimality and hypotonia (Huisman et al. 1995). In a smaller cohort from the Netherlands, perinatal exposure to background dioxin levels was associated with enhanced neuromotor maturation (Ilsen et al. 1996).

Epidemiological studies that explore the relationships between neurological development and PHDH exposure must be evaluated with a great deal of caution (Kimbrough 1997). All of the studies performed to date have had methodological problems. In the Lake Michigan and North Carolina studies, the quantitation of PHDH exposure was weak. Although maternal serum, cord blood and breast milk were collected in these studies, analytical data were not available for many samples and PCB levels were often estimated. Analytical methods were crude (low resolution packed-column chromatography), individual congeners were not quantified,

and detection limits were too high to enable quantification of the trace concentrations of PCBs present in many samples. In none of the studies was the lipid content of serum considered when PCB levels were evaluated, although this is an important determinant of PCB concentrations in biological tissues (Phillips et al. 1989). Variability of quantitation at low concentrations of PCBs is a fundamental problem in these studies, and the small differences of PCB concentration measured (or merely estimated!) were probably meaningless (Kimbrough 1997). The Lake Michigan study was further weakened by an inadequate explanation of methodology, possible selection bias, and inadequate control of possible confounding factors (Middaugh et al. 1997). A problem common to all of the epidemiological studies was the inability to rule out the influence of other chemicals or environmental factors that might have been correlated with exposure to PHDHs.

In conclusion, the epidemiological evidence for neurodevelopmental toxicity following background exposure to PHDHs is weak. The weight of the evidence suggests that exposure to low levels of PHDHs (or an environmental correlate) might possibly be associated with a slight detriment to neurological development in infants, but due to the methodological difficulties inherent to epidemiological studies this link may never be conclusively demonstrated. Severe neurological effects have never been observed in children in any epidemiological study that has investigated PHDH exposures at levels comparable to those encountered by Alaskans through the marine food chain.

Studies related to Human Health and PCBs in the Arctic

There is concern for the welfare of humans that consume large quantities of animals from the top of aquatic food chains, due to their potential exposure to PHDHs and other bioaccumulative contaminants. Some indigenous peoples from the arctic consume large quantities of fish and/or marine mammals, and these organisms have the potential to bioaccumulate organic con-taminants. Several studies have been conducted to assess the extent of organochlorine contamination in arctic food chains, and the possible human health implications for consumers of traditional foods from the marine environment.

A recent study conducted by the Centers for Disease Control, the Alaska Native Health Board and the Alaska Area Native Health Service determined the levels of PCBs and other organochlorines in the serum of 126 Alaska Native women (Rubin et al. 1997). The levels of environmental chemicals found in the serum of breast cancer patients were compared with the levels observed in women without breast cancer. The mean year of serum collection was 1985, and the serum was banked 3-8 years prior to breast cancer diagnosis. The mean serum level of PCBs found in the 126 women was 4.6 parts per billion (ppb), with 17.7 ppb being the highest individual value.

This mean value of serum PCBs in Alaska Native women is at the low end of published values for human exposures in the United States, as mean serum levels throughout the country usually average between 4 and 8 ppb (ATSDR 1993). After accounting for other risk factors for breast cancer in Alaska Natives, no relationships between breast cancer incidence and exposure to

environmental chemicals were observed in this study. This study was an excellent preliminary effort to examine possible relationships between exposure to organochlorines and disease incidence in Alaskans, and more research is needed in this area.

Inuit communities from arctic Québec have a heavy reliance on marine species consumption, and their exposure to PHDHs has been investigated. In one study, breast milk fat from the Inuit women of east Hudson Bay contained an average of 1 ppm PCBs (as summed congeners), which was similar to the PCB concentration found in beluga blubber from the region (Dewailly et al. 1993).

The researchers in the Inuit study have analyzed and presented what appears to be the same set of samples in a variety of different ways (Table 4). Average concentrations of PCBs in breast milk fat of Inuit women were 6.7 times higher than PCB concentrations found in breast milk fat of 96 Caucasian women from southern Québec, when expressed as summed PCB congeners (Dewailly et al. 1993).

In an earlier paper, data were expressed in terms of Aroclor 1260 as calculated from 2 PCB peaks. Using this method, the average concentrations of PCBs in Inuit and Caucasian breast milk fat were 2.9 and 0.52 ppm, respectively: a 5.6-fold difference (Dewailly et al. 1992). The data were also expressed as TCDD-equivalents for the dioxins, furans and non-ortho PCB congeners measured. Using that method, the average TEQs in Inuit and Caucasian breast milk fat were 51 and 23 ppt, respectively: a 2.2-fold difference (Dewailly et al. 1992).

Finally, in a later paper the data were expressed as TCDD-equivalents for the

dioxins, furans, and the non-, mono-, and di-ortho PCB congeners that were measured. Using that method, average total calculated TCDD-equivalents were three times greater in breastmilk fat of Inuit women compared to Caucasian women from southern Québec (128 and 43 ppt TCDD-equivalents respectively) (Dewailly et al. 1994). In that study, TEQs were calculated with use of TEFs for PCBS suggested by Safe (Safe 1990), which included a TEF of 0.001 for 2,3',4,4',5-pentachlorobiphenyl (PCB 118). Consideration of biological evidence subsequently led to the revision of the TEF for PCB 118 to 0.0001 (Ahlborg et al. 1994; Safe 1994b). Use of the more current TEF for PCB 118 would reduce the calculated TCDD-equivalents in Inuit and Caucasian breastmilk fat to 75 and 27 ppt respectively.

Although PCB exposure was greater in Inuit women relative to Caucasian women, differences in exposure to polychlorinated dioxins and furans were slight between the two populations. The results demonstrate how data interpretations and study conclusions can vary based upon the type of PHDH analysis chosen. When comparing between studies, large differences can be produced by different analytical and instrumental techniques. In this example the only differences were as a result of different methods of analysis, interpretation and presentation of data from the same samples!

The results of the above study have been interpreted to evidence a "surprisingly high organochlorine body burden" (Dewailly et al. 1993) in Inuit women, as a result of receipt of "an unusually high dose of dioxin-like compounds through their traditional diet" (Ayotte et al. 1996b). We feel that the degree of elevation of PHDH

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levels in the Inuit has been overstated. The average levels of PCBs reported in milk fat of these Inuit women (1 ppm expressed as summed congeners) were not elevated above the average background levels found in human milk fat in industrial countries throughout the world, which average 0.5 to 1.5 ppm PCBs (Jensen 1991a). When expressed as total TEQs, the levels of PHDHs were similar in Canadian Inuit breast milk fat and in background breast milk fat from women in the Netherlands (67 ppt and 61 ppt respectively, Figure 2) (Dewailly et al. 1992; Koopman-Esseboom et al. 1994a).

Placenta collected from Inuit women giving birth in arctic Québec in 1995 did not exhibit PHDH-mediated elevated ethoxy-resorufin *o*-deethylase (EROD) activity in comparison to women from Southern Québec (Ayotte 1996a). Elevation of EROD activity is a sensitive subclinical response to PHDH exposure, and the fact that the "PCB body burden of Inuit women may not be high enough to induce EROD activity" lends support to our interpretation that the severity of their contaminant exposure has been overstated. Interestingly, elevated EROD activity was observed in some women from both arctic and southern Québec, and that response was directly attributable to maternal cigarette smoking.

The Alaska Division of Public Health is concerned that the above reports of PCBs in breast milk fat from Canadian Inuit women may cause undue alarm among Native Alaskans and discourage the breastfeeding of infants. We would like to emphasize the important nutritional, immunological and social benefits of breast feeding. Breast milk has anti-infective properties that protect the infant from various infections in the early months of life, and breast-fed infants are less likely to get colic, infantile allergies, and eczema than are formula-fed infants (Hofvander 1991). Breast feeding is also associated with a reduced risk of otitis media development in children (Infante-Rivard et al. 1993). The consensus of most experts is that the risks associated with global background chemical contamination in breast milk are far outweighed by the known benefits of breast feeding (Jensen et al. 1991b).

Another research group investigated the comparative risks and benefits of traditional native diets in Canada. Their approach focused on a documentation of dietary intake, complemented by detailed chemical analysis of traditional food items for their content of both nutrients and environmental contaminants. A community in the Baffin Islands was chosen as a sentinel population for study, due to a heavy reliance on marine species consumption by the inhabitants.

In an initial study of the community on Broughton Island (Kinloch et al. 1988), the average daily intake of PCBs (as summed congeners) was calculated to be 74 μg/day per individual. Although PCB concentrations were low in most food items, marine mammal blubber and skin was found to contain over 1 ppm PCBs. Consumption of various food items and dietary PCB intake were found to vary seasonally. No correlations were observed between calculated PCB intakes based on food consumption and actual PCB blood levels in individuals.

Interestingly, three of four breast milk samples contained PCBs within the same range reported for average southern Canadian women (13, 16 and 19 ppb PCBs

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in whole milk, in comparison to the southern Canadian average of 15.9 ppb PCBs in whole milk). A breast milk sample from a fourth Inuit woman contained 69 ppb PCBs in whole milk, which was above the Canadian 'tolerable level' of 50 ppb PCBs in whole milk. A larger follow-up study (Kinloch et al. 1992) documented the substantial nutritive value of traditional foods in the Inuit community.

Although marine mammal blubber samples were found to contain the greatest PCB concentrations among the traditional foods studied, blubber was also documented to be an excellent and important source of retinol and omega-3 fatty acids for the Inuit diet. A balanced approach was urged toward the assessment of traditional food safety. Health risks might well be associated with a decreased reliance on traditional foods in native communities and a concomitant decline in nutritional status.

Results from the above community on Broughton Island should not be extrapolated to represent the Canadian indigenous situation in general, or the situation in Alaska. The Broughton Island community was non-randomly selected from harvest data as a population with a relatively high risk of PCB contamination, and was intended to represent a worst-case scenario among the Inuit (Kinloch et al. 1988). Organochlorine exposure in the Broughton Island Inuit has been compared with that of two Sahtú Dene/Métis communities from western Canada that relied heavily on traditional foods from a terrestrial food chain (Kuhnlein 1995a; Kuhnlein et al. 1995b). Exposure to PCBs and other organochlorines was found to be very low in the Sahtú Dene/Métis, and no traditional food item of the Sahtú Dene/Métis was found to contain over 0.1 ppm PCBs.

Traditional foods of the Sahtú Dene/Métis contained an abundant supply of many nutrients, and contributed much more protein, iron, zinc, magnesium and copper to the diet than did market foods (Kuhnlein 1995a). It should not be assumed that dietary intake of PCBs is elevated in Native Alaskan communities. Rather, research is needed to determine the levels of exposure to PHDHs in Alaskan communities before risks can be assessed.

Risk Assessment for the Consumption of Subsistence Foods in Alaska

For the present purpose, risk assessment involves the consideration of toxicity, exposure scenarios and chemical concentration data in order to evaluate the safety of subsistence food consumption. When developing consumption-oriented recommendations for public health purposes, it is also critical to evaluate the beneficial aspects of traditional food consumption. These include physical health benefits such as an apparent reduced risk of heart disease due to the omega-3 polyunsaturated fatty acids found in fish and marine mammals, as well as the benefits of exercise associated with the harvest of traditional foods. There are also important social and cultural benefits associated with the harvest, sharing and consumption of traditional foods (Usher et al. 1995).

In addition, it is important to perform a relative risk assessment between traditional foods and the market foods that would replace them in the Alaskan Native diet. For example, risks associated with trace contaminants in traditional foods should be compared against the risks associated with a reduced nutrient intake or an increased intake of saturated fats associated with

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market food consumption. A nutritional study has demonstrated the superior nutritional quality of traditional foods in the Alaskan Native diet, and these foods were hypothesized to play a protective role against chronic diseases in the Alaskan Native population (Nobmann et al. 1992). Since concentrations of coplanar PCB congeners, dioxins or furans have not yet been determined in Alaskan subsistence foods, the following risk assessment will focus on the summed PCB congener data that is available.

When a chemical is associated with both carcinogenic and non-carcinogenic health effects, the USEPA conducts two separate risk assessments based on the two types of endpoints (USEPA 1994). Both types of risk assessments have been performed by the USEPA for PCBs. The USEPA's risk assessment of carcinogenicity was based on studies with rats treated with high doses of the commercial PCB mixture Aroclor 1260 (25 to 100 ppm). For PCBs, the carcinogenic endpoint was calculated to be more sensitive than chronic systemic endpoints such as reproductive, developmental and immunological health. The reason why the carcinogenic endpoint turned out to be the most sensitive is that the USEPA uses a very conservative method to calculate the risks posed by environmental carcinogens. With their approach, it is assumed that there is no threshold below which an increased cancer risk does not occur. Extrapolation of effects from high-dose laboratory studies to low environmental levels is based on a linearized multistage no-threshold model. This approach has been widely criticized because it is unrealistically conservative and fails to take evidence of thresholds for carcinogenic endpoints into account, particularly for chemicals that act through a promotion mechanism such as PHDHs (Ames et al. 1987; Shu et al. 1987; Hanson 1991; Covello et al. 1993). For the carcinogenic endpoint, the USEPA has adopted a high risk and persistence upper-bound slope factor of 2.0 per (mg/kg)/day for PCBs (IRIS 1996). The USEPA concedes that this slope factor drives a currently recommended seafood screening value for PCBs that "will result in widespread exceedance in waterbodies throughout the country and will drive virtually all fish and shellfish contaminant monitoring programs into the risk assessment phase for PCBs" (USEPA 1995).

In our opinion, a risk assessment for PHDHs based on chronic systemic endpoints such as reproductive, developmental and immunological health is more appropriate than a risk assessment based on a carcinogenic end point, because the chronic end point risk assessment has a stronger foundation of scientific evidence behind it. Animal cancer studies were performed at high doses, at which the mechanisms of carcinogenicity may have involved cell proliferation as a result of cellular toxicity. This mechanism of toxicity would not be applicable to low-dose exposures. Furthermore, the linearized multistage no-threshold model used for extrapolation is inappropriate for use in PHDH risk assessment. The USEPA's focus on carcinogenicity as the most sensitive endpoint for PHDHs is not in accordance with human epidemiological evidence or laboratory animal studies, which both suggest that developmental and immunological deficits may occur at lower PHDH doses than does cancer (Hanson 1991; DeVito et al. 1995). Therefore, for the remainder of this paper our risk assessment will focus on chronic systemic health endpoints of PCB exposure, using a

very conservative approach with a large margin of safety.

In order to determine the non-carcinogenic risks associated with PHDH exposure, the USEPA considered a large body of literature related to chronic, developmental, immunological and neurobehavioral toxicity from human epidemiological and animal studies. Risk calculations were performed using data from the strongest studies that showed effects at the lowest doses. The analysis was ultimately based on data from a study in which adult female monkeys were fed low doses of PCB (Aroclor 1254) over a long period of time (ongoing; over 4 years). At the lowest dose tested, 0.005 mg/kg/day, subtle ocular effects were observed such as eye exudate, inflammation and/or prominence of the eyelid. The monkeys also exhibited changes in finger and toe nails, and some changes in immunological parameters were observed such as decreased IgG and IgM levels (IRIS 1996).

To calculate the daily reference dose that is likely to be without an appreciable risk of deleterious effects during a lifetime, this lowest observable adverse effect level (LOAEL) of 0.005 mg/kg/day was divided by a safety factor of 300. This safety factor included a factor of ten to protect the most sensitive members of the population, and three factors of 3 to account for uncertainties associated with (1) the extrapolation of data from monkeys to humans, (2) from subchronic toxicity to lifetime chronic exposure, and (3) the fact that a LOAEL was used instead of a NOAEL (no observable adverse effect level). By this conservative approach, a oral reference dose (RfD) of 2×10^{-5} mg/kg/day was derived.

The maximum allowable daily fish consumption was calculated from the reference dose using the following equation:

$$CR_{lim} = [RfD \bullet BW] / C_m$$

where

CR_{lim} = maximum allowable daily consumption rate of the fish species (kg/d)
RfD = reference dose
BW = consumer body weight (kg)
C_m = measured concentration of contaminant m (mg/kg)

A body weight of 70 kg was used in our calculations, which is the average weight of an adult male.

Figure 3 illustrates the calculated daily consumption limits that would result for the freshwater fish species from Schrader Lake, Alaska, based on the analysis of samples collected in 1992 (Table 1) (Wilson et al. 1995). Dietary surveys have revealed that Native Alaskan adults consume an average of 4 ounces of fish and shellfish daily, which is six times greater than the U.S. national average (Nobmann et al. 1992). The concentrations of PHDHs in Schrader Lake fish are so low that they are very safe to eat, even at the high rates of consumption typical for rural Alaskan communities.

The limited data available for Alaskan marine mammal tissue concentrations (Table 1) were subjected to a risk assessment. In this analysis we focused on the consumption of blubber, as this tissue contains the highest concentration of PCB-like compounds. Since marine mammal tissue is consumed by Alaskan Natives much less frequently than are fish or shellfish (Nobmann 1989), a maximum monthly consumption limit was calculated rather than a daily consumption limit. The monthly

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consumption quantity of Alaskan marine mammal blubber deemed safe by USEPA standards was quite low. We compared the USEPA risk assessment method with the PCB intake standard utilized in Canada (Figure 4). The Canadian Tolerable Daily Intake of PCBs is 1 μg/kg/d (Kuhnlein 1995a). This value is fifty-fold higher (less conservative) than the USEPA reference dose of 0.02 μg/kg/d, but still incorporates a 5-fold safety factor above the lowest observed adverse effect level for PCBs from animal studies (ocular effects and distorted nail growth in monkeys). These results demonstrate how dramatically the risk assessments performed by different governmental agencies can vary, and how relevant these differences are to Native Alaskan subsistence food safety issues. Using the reasonable Canadian guidelines, it is apparent that most blubber from Alaskan marine mammals can be safely consumed in large quantities.

It is important to keep a relative perspective on the levels of PCBs found in Alaskan fish and marine mammals. The concentration of PCBs found in Alaskan beluga whale blubber was similar to the PCB concentration found in Steelhead trout from the Manistee River, Michigan in 1990, while concentrations of PCBs in blubber from other Alaskan marine mammals were often similar to or below the levels found in fish from the Great Lakes (Table 5).

In a recent survey of PCB concentrations in sediments and liver of bottom-feeding fish from bays of the U.S. West Coast, fish from Alaska and Oregon were significantly less contaminated than fish from California and Washington (Varanasi et al. 1989). Blubber PCB levels of most marine mammals in Alaska are far lower than the

PCB levels found in blubber of long-finned pilot whales hunted near the Faroe Islands. Mean PCB levels (total PCBs quantified by Aroclor matching) in the blubber of 53 Faroe Islands long-finned pilot whales harvested in 1986 were 20 ppm (20,000 ng/g) wet weight (Simmonds et al. 1994). Mean DDE levels in the blubber (12 ppm wet weight) (Simmonds et al. 1994) and mean methyl mercury levels in various tissues (Julshamn et al. 1987) were also elevated in long-finned pilot whales from the Faroe Islands. Pilot whale tissue is commonly consumed by the people of the Faroe Islands, and comprehensive studies of their health are currently being conducted. The results of these studies will be of great interest, as they will likely present a "worst-case" scenario for any possible health risks associated with subsistence food consumption in Alaska.

Congener- and Species-Specific Data Gaps

Studies of PHDH content in Alaskan subsistence foods should initially focus on marine mammal species of most concern. Additional information is needed on PHDH levels in belugas, which are rather high in Alaska. Data from Point Lay belugas suggest that PHDH levels may be greater in male than female belugas. However, in belugas sampled from the South Beaufort Sea in Canada, PHDHs were high in both males and females (Muir 1996a). This is of concern because belugas from the Mackenzie River Delta and Beaufort Sea migrate to Alaskan waters and are hunted by Alaskan natives along the north slope (Robert Suydam, personal communication). Concentrations of PHDHs were lower in belugas from Cook Inlet than in belugas from the Chukchi Sea. Further research is needed to clarify the relationship between

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PHDH contamination, location, sex and age in belugas.

Research should also focus on the ringed seal and bearded seal, since they are consumed so commonly by Alaskan natives. A determination of TEQs in ringed seal blubber following analysis for coplanar congeners is particularly needed.

Another marine mammal species that should be a primary focus is the Pacific Walrus. There are currently no quality PHDH data available for Pacific Walrus in Alaska, yet they are being hunted for subsistence food use. In the Canadian arctic, it was discovered that some Pacific Walrus had unexpectedly high concentrations of PHDHs in blubber (Muir et al. 1992b). Walrus at Inukjuak with high PHDH concentrations (5260 ng/g wet weight) were thought to have been feeding at a higher trophic level than usual, and predation on ringed seals was suspected. Although seal predation was once thought to be an uncommon behavior confined to large male walrus, the behavior may be more common than previously believed. Since seal predation has also been observed in Pacific Walrus in Alaska (Lowry et al. 1984), PHDH levels may be high in Alaskan walrus as well.

Additional information is needed on blubber PHDH concentrations in Northern Fur Seals. A recent study has measured comparatively high PCB levels in fur seals in Alaska, which the authors speculated may have been due to their higher trophic level and more extensive annual migrations in potentially contaminated areas relative to other Alaskan seal species (Krahn et al. 1997).

Finally, a sixth marine mammal that warrants focused research is the Stellar sea lion. Although few samples have been analyzed, available data indicate that Stellar sea lion blubber contains the highest PCB concentrations among marine mammals in Alaska. Stellar sea lions have the potential to bioaccumulate higher levels of organic contaminants, because they sometimes have a marine mammal component to their diet. Stellar sea lions are known to eat northern fur seal pups, sometimes in large numbers (Hoover 1988). There is also speculation that Alaskan Stellar sea lions may become exposed to PCBs along their migration route, which encompasses offshore areas of southern California (Varanasi et al. 1993). The Stellar sea lion is declining rapidly in numbers, and should not be taken solely for research purposes. However, sea lions are taken for subsistence use and PHDH levels could be determined in hunted animals.

The use of "total PCB" concentrations during the risk assessment process imposes an error on subsequent estimates of the toxicity of environmental samples. "Total PCBs" generally do not include or consider the coplanar PCBs, dioxins or furans in environment samples. These planar congeners can represent a significant proportion of the total PHDH toxicity in terms of TEQs. Estimates of risk can vary significantly, depending on whether total PCBs or calculated TCDD-equivalents from coplanar PHDH congeners are used. For example, the derived potency (with use of USEPA risk assessment procedures) of a PCB mixture extracted from Great Lakes salmon was 3.7 times greater when calculated as TEQs from coplanar PCBs than when calculated as total PCBs based on Aroclor pattern matching (Williams et al. 1992). The problem becomes even more severe when "total PCBs" are used to compare the relative toxicity of various

subsistence foods from the marine environment. Patterns of PCB congeners vary significantly among arctic marine species, and these patterns may profoundly influence their overall toxicity.

The relative abundance of various PCB congeners in the arctic environment and biota have been determined. In arctic cod from Canada, the pattern of PCB congeners was remarkably similar to an Aroclor standard mixture (1242:1254:1260, 0.6:3:1) (Muir et al. 1988). Lower-chlorinated congeners such as penta- and hexa-chlorobiphenyls were well represented in the arctic cod samples. In contrast, these lower-chlorinated congeners were less common in ringed seal blubber, and were virtually absent in polar bear fat. PCB congener profiles of ringed seal and polar bear were dominated by higher-chlorinated congeners such as hepta-, octa- and nona/decachlorbiphenyls. These data indicate that the ringed seal and polar bear were able to preferentially metabolize and eliminate the lower-chlorinated PCB congeners, in contrast to the arctic cod which could not. Interestingly, PCB congener profiles from narwhal and beluga blubber resembled those from cod, and contained a substantial proportion of lower-chlorinated congeners (Norstrom et al. 1994).

Differences in PCB congener profiles among marine species have been attributed to differences in metabolic capabilities related to specific cytochrome P450 enzymes. Small cetaceans such as dolphin, porpoise, beluga and narwhal do not metabolize PCBs with adjacent non-chlorinated *meta* and *para* positions efficiently. This deficiency in cetaceans has been attributed to a low activity of CYP 2B, the enzyme responsible for metabolism of

most PCB congeners in higher animals (Tanabe et al. 1988).

Patterns of coplanar PHDH congeners also vary among marine species, and their relative contributions to TEQs vary accordingly. In general, concentrations of non-ortho PCBs were similar between narwhal, beluga and ringed seal from the Canadian arctic (Ford et al. 1993). In contrast, concentrations of mono-ortho PCBs were much greater in narwhal and beluga than in ringed seal. Chlorinated dioxins and furans were found to contribute 37 to 42% of total TEQs in ringed seals, but less than 5% of total TEQs in narwhal and beluga (Ford et al. 1993). Another study confirmed that beluga have an exceptional ability to metabolize non-ortho PCB congeners and TCDD (Norstrom et al. 1992), a capacity attributed to high levels of CYP-1A activity in cetaceans (Watanabe et al. 1989).

Metabolic differences and subsequent PHDH congener profiles can have a dramatic influence on the toxicity of PHDH mixtures found in arctic animals. The implications of these differences for our risk assessment may be profound. In particular, it is possible that our risk assessment may have overestimated the relative toxicity of beluga blubber but underestimated the relative toxicity of ringed seal blubber. This is because beluga blubber is likely to contain a lower proportion of the most toxic coplanar PHDH congeners than ringed seal blubber does.

Due to this dilemma, it might seem that congener-specific coplanar analyses are necessary in order to estimate the true toxicity of PHDH mixtures in environmental samples. This is a rather regrettable conclusion, because congener-specific

coplanar analysis is difficult and expensive. Fortunately, there may be an acceptable alternative. Total PCB measurements can be correlated with TEQs in specific species from specific systems. Following an initial investigation of the relationship, total PCBs have been used successfully to predict TEQs within a defined system (Williams et al. 1992).

The risk assessment process for PHDH content in arctic subsistence foods would greatly benefit from the establishment of such relationships. However, these congener-specific relationships must be determined on a location-by-location basis, because there is major geographic variability in the ratio of TCDD to total PCBs among arctic marine mammals (Norstrom et al. 1990).

Summary

Traditional foods are an important and healthful component of the diet of Native Alaskans, and the Division of Public Health strongly endorses the consumption of subsistence foods. The limited data that are available for PCB concentrations in subsistence foods suggest that most Alaskan fish and seafood is less contaminated than fish from the Lower 48, which reflects the relatively pristine environment of Alaska. The benefits of a traditional food diet far outweigh the relative risks posed by the consumption of trace quantities of PHDHs in traditional foods. We encourage the consumption of a varied diet consisting of a number of different species. Exposure to PHDHs can be lessened by choosing animals from a lower trophic level (for example, baleen whales rather than toothed whales) and by avoidance of older male animals. Additional information should be

obtained regarding the PHDH content of the beluga whale, ringed seal, bearded seal, Pacific walrus, northern fur seal and Stellar sea lion.

Alaska Natives that have traditionally consumed marine mammals in their diet should continue to enjoy their foods, including the consumption of marine mammal blubber. Marine mammal blubber is an excellent source of monounsaturated fatty acids, omega-3 fatty acids, and fat soluble vitamins. The Alaska DHHS believes that the risks associated with avoidance of marine mammal blubber consumption may be greater than the small element of risk of subtle health effects associated with the presence of PHDHs in blubber. For example, avoidance of marine mammal blubber and replacement with foods high in saturated fat (such as Crisco, fat products from cattle and pigs, and dairy products such as butter and cheese) could increase the prevalence of heart disease, diabetes, and certain cancers in Alaska Natives.

Our analysis has identified key knowledge gaps that should be addressed in future studies of subsistence food safety. There is a pressing need to obtain additional information regarding PCB concentrations in Alaskan subsistence foods and sport fish. Existing data regarding PCB concentrations are minimal and scattered. The State of Alaska needs support to conduct a comprehensive sampling and analysis program to evaluate subsistence food safety. We need to obtain location-specific information on the PCB content of subsistence foods throughout the state.

We need information about which subsistence species are most contaminated, and what differences in PCB levels exist as

a function of the age, sex or tissue type of the animals. In addition, it would be helpful to evaluate how various preparation methods influence PCB levels in subsistence foods as they are actually consumed by people. We need to refine our chemical analyses and obtain congener-specific information, including data on coplanar congeners, dioxins and furans. The relationship between total PCBs and specific coplanar congeners should be determined for each marine animal species consumed by Alaskan Natives in order to improve future risk assessments and estimates of toxicity.

Finally, Alaska has a critical need to examine human biomarkers of PCB exposure. At present, information regarding PCB concentrations in the serum of Alaskan Natives is limited, and we have no information about PCB concentrations in the adipose tissue or breast milk of Alaskans. This information would provide public health officials with the most relevant data possible regarding PCB exposure through the subsistence food chain. A comprehensive screening study should be performed throughout the state.

Table 1. PCB concentrations in Alaskan marine mammals and freshwater fish (summed congeners, ng/g wet weight)

Species	Location	Collection Date	Tissue	Sex	n	ΣPCB[1]		Reference
Beluga Whale	Pt. Lay, Chukchi Sea, AK	1990	Blubber		10	3,808.1	(1,496.4)	Schantz et al. 1993
Beluga Whale	Pt. Lay, AK	July 1992	Blubber	F	5	680	(216)	Tarpley, 1994
				M	2	2,986-6,406		
Beluga Whale	Cook Inlet	1992-95	Blubber		12	977	(484)	Becker et al. 1997a
Bowhead Whale	Barrow, AK	1992	Blubber		11	689	(226)	Becker, 1993a
Gray Whale	Kodiak Island, AK Tugidak Island	May-June 1989	Blubber Liver		2	150-1,200 79-880		Varanasi et al. 1994
Ringed Seal	Barrow, AK	July 1988	Blubber Liver Kidney		2	686-686 18-28 10-17		Schantz et al. 1993
Ringed Seal	Nome, AK	May 1989	Blubber Liver		2	371-415 8-9		Schantz et al. 1993
Ringed Seal	Bering Sea, AK	May 1989 & 94 May 1993-95	Blubber Blubber	F M	2 6	330-363 249	(75)	Krahn et al. 1997
Northern Fur Seal	St. Paul Island, AK	July 1987	Blubber Liver Kidney Muscle		2	275-590 18-48 17-87 14-30		Schantz et al. 1993
Northern Fur Seal	St. Paul Island, AK	July 1990	Blubber	M	7	1,343	(522)	Krahn et al. 1997
Northern Fur Seal	Alaska	1990	Liver Blubber		9 9	150 2,100	(69) (1,080)	Varanasi et al. 1993
Harbor Seal	Prince William Sound, AK	September 1993	Blubber	F M	2 3	225-240 599	(143)	Krahn et al. 1997
Harbor Seal	Alaska	1989-1990	Liver Blubber		9 7	21 340	(6) (110)	Varanasi et al. 1993
Bearded Seal	Bering Sea, AK	May 1993-95	Blubber	F M	1 5	199 153	(110)	Krahn et al. 1997
Steller Sea Lion	Alaska	1976-1978	Blubber Liver	M F M F	12 17 13 15	12,580 4,346 513 236		Lee, 1996
Steller Sea Lion	Alaska	1985, 1989, 1990	Liver Blubber		8 8	290 23,000	(340) (37,000)	Varanasi et al. 1993
Lake Trout	Schrader Lake, AK (inland)	August 1992	Muscle Liver		11 5	6.6 22.8		Wilson et al. 1995
Grayling	Schrader Lake, AK (inland)	August 1992	Muscle Liver		5 5	1.3 3.2		Wilson et al. 1995

1 = Mean value with standard deviation in parenthesis when n > 2 (when available)
Both actual values listed when n = 2

Table 2. PCB concentrations in Canadian marine mammals and fish (summed congeners, ng/g wet weight)

Species	Region	Collection Date	Tissue[1]	Sex	N	SPCB		Reference
Ringed seal	W Hudson Bay	1992	B	F	24	1115	(425)	Muir, 1994a
Ringed seal	W Hudson Bay	1992	B	M	35	1852	(1359)	Muir, 1994a
Ringed seal	E Baffin Is	1994	B	F	10	467	(195)	Muir, 1994a
Ringed seal	E Baffin Is	1994	B	M	10	675	(597)	Muir, 1994a
Ringed seal	E Hudson Bay	1989-92	B	F	6	1457	(1648)	Muir, 1994a
Ringed seal	E Hudson Bay	1989-92	B	M	4	1234	(636)	Muir, 1994a
Ringed seal	Lancaster S	1993	B	F	10	535	(154)	Muir, 1996a
Ringed seal	Lancaster S	1993	B	M	10	655	(184)	Muir, 1996a
Ringed seal	Admirality Inlet	1983	B	M	10	794	(879)	Muir et al, 1988
Ringed seal	Admirality Inlet	1983	B	F	16	308	(138)	Muir et al, 1988
Ringed seal	Admirality Inlet	1975-76	B	F	5	600	(99)	Muir et al, 1988
Ringed seal	Barrow Strait	1984	B	M	19	568	(287)	Muir et al, 1988
Ringed seal	Barrow Strait	1984	B	F	14	375	(172)	Muir et al, 1988
Ringed seal	Barrow Strait	1984	L	M	19	6	(4)	Muir et al, 1988
Ringed seal	Barrow Strait	1984	L	F	14	4	(3)	Muir et al, 1988
Ringed seal	Arviat	1991	B	M	13	1760	(1200)	Muir, 1993a
Ringed seal	Arviat	1991	B	F	9	846	(310)	Muir, 1993a
Walrus	E Hudson Bay	?	B	F	3	5604	(1941)	Muir, 1994a
Walrus	E Hudson Bay	?	B	M	2	10403	(13916)	Muir, 1994a
Beluga	Western Greenland	?	K	M	10	169	(60)	Muir, 1993a
Beluga	Western Greenland	?	K	F	10	75	(38)	Muir, 1993a
Beluga	Western Greenland	?	T	M	10	323	(265)	Muir, 1993a
Beluga	Western Greenland	?	T	F	10	411	(178)	Muir, 1993a
Beluga[2]	MacKenzie Delta	?	B	F	5	5299	(1460)	Muir, 1996a
Beluga[2]	MacKenzie Delta	?	B	M	20	4882	(1878)	Muir, 1996a
Beluga[2]	MacKenzie Delta	?	T	F	5	218	(60)	Muir, 1996a
Beluga[2]	MacKenzie Dalta	?	T	M	6	317	(96)	Muir, 1996a
Beluga	E Hudson Bay	1984-85	B	M	8	2770	(510)	Muir et al, 1990
Beluga	E Hudson Bay	1984-85	B	F	8	1230	(840)	Muir et al, 1990
Beluga	W Hudson Bay	1986	B	M	4	3120	(340)	Muir et al, 1990
Beluga	W Hudson Bay	1986	B	F	4	960	(1000)	Muir et al, 1990
Beluga	Cumberland Sound	1983	B	M	6	4910	(250)	Muir et al, 1990
Beluga	Cumberland Sound	1983	B	F	6	1150	(410)	Muir et al, 1990
Beluga[2]	Beaufort Sea	1983, 1987	B	M	10	3330	(850)	Muir et al, 1990
Beluga[2]	Beaufort Sea	1983, 1987	B	F	2	830 - 1640		Muir et al, 1990
Beluga	Jones Sound	1984	B	M	8	2530	(570)	Muir et al, 1990
Beluga	Jones Sound	1984	B	F	7	2460	(1980)	Muir et al, 1990
Beluga	St Lawrence Estuary	1986-87	B	M	4	75800	(15300)	Muir et al, 1990
Beluga	St Lawrence Estuary	1986-87	B	F	5	37300	(22000)	Muir et al, 1990
Arctic char	Cornwallis Island	1991	M		12	72.5	(40.4)	Muir & Lockhart, 1993b
Arctic char	Alex Heiberg	1992	M		10	6.8	(2.7)	Muir & Lockhart, 1993b
Arctic char	Resolute	1993	M		5	290	(118)	Muir & Lockhart, 1993b
Arctic char	W Hudson Bay	1994	M		6	11.4	(3.5)	Muir & Lockhart, 1996b
Burbot	Yellowknife	1993	L		5	26.9	(18.0)	Muir & Lockhart, 1994b
Burbot	Mackenzie River	1994	L		11	56.6	(18.1)	Muir & Lockhart, 1996b
Lake trout	Banks Island	1993	M		5	31.9	(15.5)	Muir & Lockhart, 1996b
Lake trout	Rankin Inlet	1993-94	M		12	19.0	(14.1)	Muir & Lockhart, 1996b
Lake trout	Banks Island	1993	M		6	33.5	(9.9)	Muir & Lockhart, 1996b
Lake trout	Mackenzie Delta	1993	M		6	8.8	(3.7)	Muir & Lockhart, 1994b
Walleye	Hay River	199?	M		3	1.4	(0.3)	Muir & Lockhart, 1996b

Mean value with standard deviation in parenthesis; both actual values listed when n = 2
1: B = Blubber, L = Liver, M = Muscle + Skin, K = Kidney, T = Muktuk
2: Shared population with Alaska

Table 3. Selected epidemiological studies of immunotoxicity in PHDH exposed humans

Nature of Exposure	n (exposed group)	Exposure Measured?	Time Between Exposure & Study	DTH[1]	CD4/CD8	IgA	IgM	Lymphocyte Proliferation	MLR[2]	Reference
Yu-Cheng incident, Taiwan. Consumption of rice oil contaminated with PCBs and furans	varied; 30-143	unclear	1 and 3 yr	* →	* →	* →	* →	* ←		Lu et al, 1985
Lactational; fish-eating population, Japan	37	yes - TEQ in breast milk 120 pg/kg median daily intake	none		* ←					Nagayama et al, 1996
Industrial workers (TCDD)	11	workers only, not controls. 43-874 ppt TCDD/blood fat	20 years		nd			nd	* →	Knutsen, 1984
Chemical plant explosion (TCDD) Seveso, Italy	45 (children)	no, but high (21 with chloracne)	2 mo, repeat every 4 mo			nd	nd	nd	nd	Pocchiari et al, 1979
Missouri - TCDD in soil	68	no	unclear; none?		→			nd		Stehr, 1986
Industrial workers - polybrominated dioxins and furans	42	workers only, not controls blood TEQ median 83 ppt	several months		nd	nd	* ←			Zober, 1992
Times Beach Missouri TCDD in soil	50	no	unclear	(in sub- → set)	nd			(in subset) →		Knutsen, 1984

* = statistically significant, p ≤ .05
nd = no difference
ppt = parts per trillion
1: delayed-type hypersensitivity
2: mixed lymphocyte response

Table 4. **Comparison of reported PHDH concentrations (ppb) in breast milk fat from the same study of Canadian Inuit and Caucasians from Southern Quebec[a]**

Analysis	Inuit n analyzed	Inuit PHDH (ppb)	Caucasian PHDH (ppb)	Inuit/ Caucasian	Reference
PCBs as Aroclor 1260	105	2900	520	**5.6**	Dewailly 1992
Dioxins, furans, & non-ortho PCBs (#77, 126 and 169)	40	.051[b]	.023[b]	**2.2**	Dewailly 1992
Sum of 10 PCB congeners (#28, 52, 101, 118, 138, 153, 170, 180, 183 & 187)	107 (but only 35 for #118, 170 & 187)	1052	157	**6.7**	Dewailly 1993
Dioxins, furans, non-ortho PCBs (#77, 126 & 169), & PCB 118 (mono-ortho) & #138, 153, 170 & 180 (di-ortho)	40 (dioxins, furans & non-ortho) 35 for 118 & 170 109 for 138, 153, 170 & 180	.128[c]	.043[c]	**3.0**	Dewailly 1994

a: Between July 1989 and July 1990, 109 Inuit women provided a milk sample. This was compared to milk obtained from women from the general population of Southern Quebec (16 pools of six women each.)

b: Summed as TCDD-equivalents (ppb).

c: Summed as TCDD-equivalents (ppb). When the currently accepted TEF value of 0.0001 is used for PCB 118 (Ahlborg et al. 1994, Safe 1994), these values are decreased to .075 and .027 ppb in Inuit and Caucasian women respectively.

Table 5. PCB concentrations in freshwater fish from the Great Lakes (mean, ng/g wet weight)

Species	Location	Collection Date	Tissue	n	PCB	Reference
Walleye	Saginaw Bay	1990	Whole fish	13	2300[1]	Giesy, 1997
Chinook Salmon	Au Sable River, Mich[3]	1990	Whole fish	1 composite of 5 fish	1700[2]	Giesy, 1994
Pike	Au Sable River, Mich[3]	1990	Whole fish	1 composite of 5 fish	720[2]	Giesy, 1994
Walleye	Au Sable River, Mich[3]	1990	Whole fish	1 composite of 5 fish	2200[2]	Giesy, 1994
Steelhead	Manistee River, Mich[3]	1990	Whole fish	1 composite of 5 fish	3900[2]	Giesy, 1994
Perch	Muskegan River, Mich[3]	1990	Whole fish	1 composite of 5 fish	770[2]	Giesy, 1994
Chinook Salmon	Lake Michigan (by Ludington MI)	1988	fillet (no skin)	81	940[2]	Williams, 1992

1 = Summed congeners
2 = Totals based on Arochlor pattern matching
3 = Great Lakes - influenced zone of river

Figure 1. **Structure, nomenclature and numbering for polyhalogenated biphenyls (a & b), dioxins (c) and furans (d).**
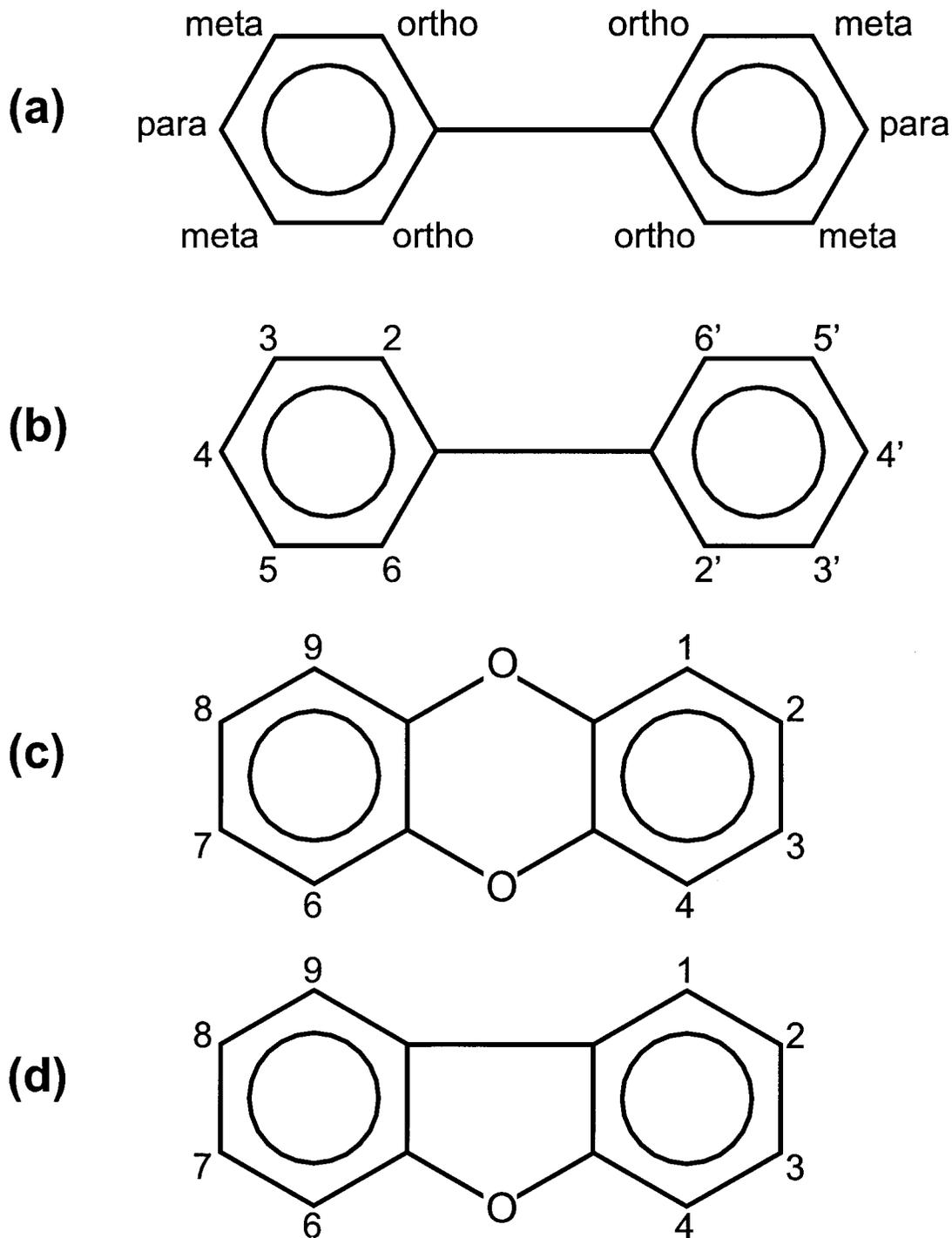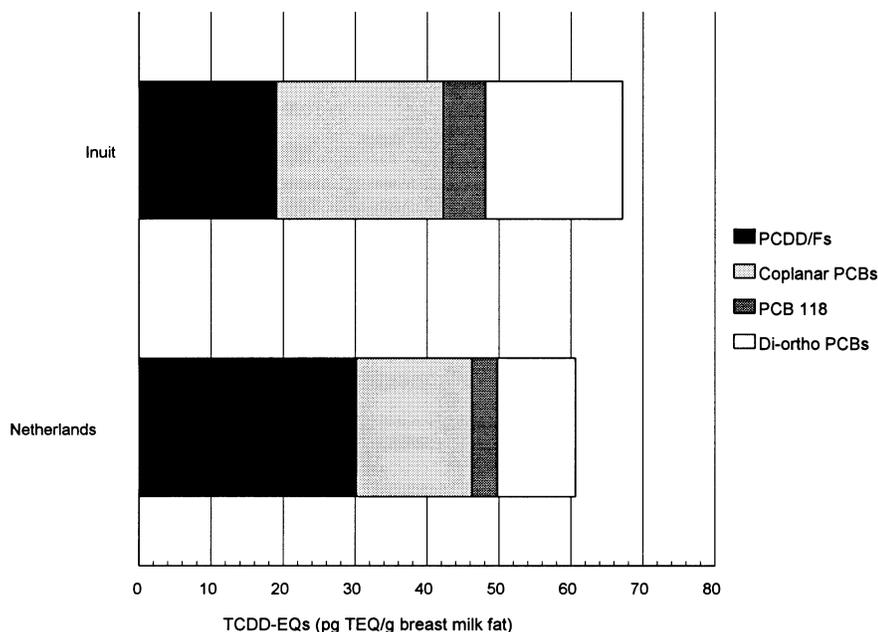
Figure 2. Direct comparison of TCDD-equivalents in breast milk fat of women from the Netherlands and Arctic Quebec, as calculated with identical congeners and TEF values.

TCDD-EQs (pg TEQ/g breast milk fat)

* TEQs calculated for all congeners that were available for both data sets. In both studies, dioxin and furan TEQs were originally calculated with use of the same International TEFs and were not re-calculated. Inuit TEQs for PCB congeners were re-calculated with use of WHO TEFs (Ahlborg et al. 1994) to provide consistency between the two studies. Dewailly's TEFs for PCB 138 and 153 were applied to the Netherlands data to provide consistency between the two studies.

* The major difference between this calculation and Dewailly's original (Dewailly et al. 1994) is due to TEF assignment for PCB 118. Dewailly originally used a TEF of 0.001, as suggested by Safe (Safe 1990). This represented a 10-fold greater toxicity as compared to the WHO TEF. Note that Safe revised his TEF in 1994 to agree with the WHO TEF of 0.0001 (Safe 1994b).

Figure 3. **Maximum allowable daily consumption* of fish flesh from Schrader Lake, Alaska based on PCB content. (chronic systemic health endpoint, USEPA)**
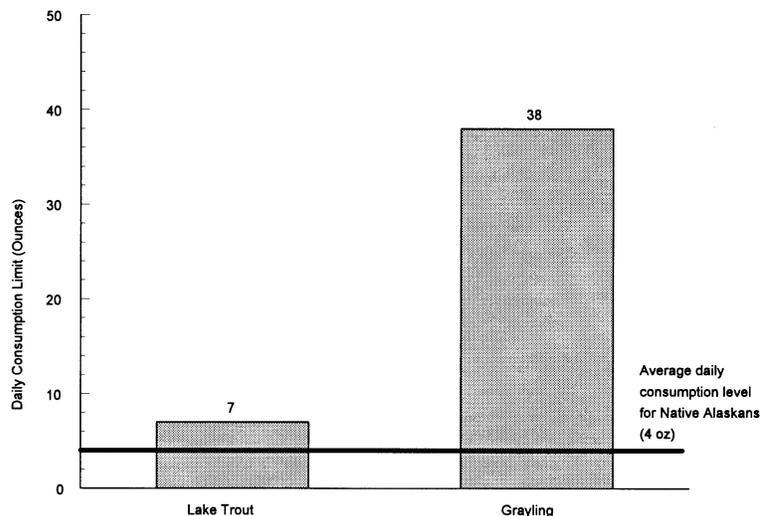
*For a 70-kg adult. Assumes daily consumption over a lifetime.

Figure 4. **Maximum allowable monthly consumption limit for Alaskan marine mammal blubber, based on total PCB content (chronic system health endpoint, for a 70-kg adult).**
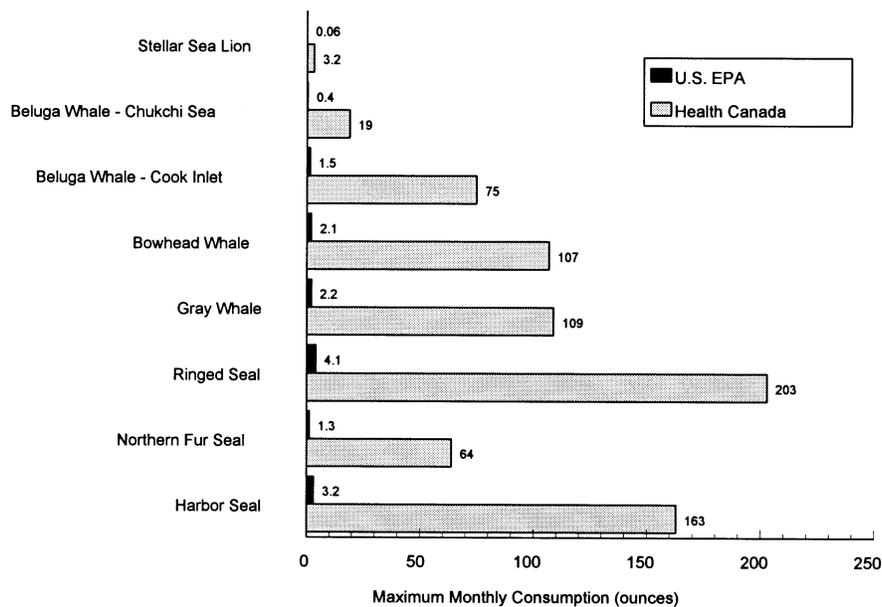
References

Adkins, E.K. (1979). "Effect of embryonic treatment with estradiol or testosterone on sexual differentiation of the quail brain." Neuroendocrinology 29:178-185.

Adkins-Regan, E. (1987). "Sexual differentiation in birds." TINS 10(12):517-522.

Aguilar, A., A. Borrell (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.

Ahlborg, U.G., G.C. Becking, L.S. Birnbaum, A. Brouwer, H.J. G.M. Derks, M. Feeley, G. Golor, A. Hanberg, J.C. Larsen, A.K.D. Liem, S.H. Safe, C. Schlatter, F. Waern, M. Younes, E. Yrjanheikki (1994). "Toxic equivalency factors for dioxin-like PCBs." Chemosphere 28(6):1049-1067.

Ahlborg, U.G., A. Brouwer, M.A. Fingerhut, J L. Jacobson, S.W. Jacobson, S.W. Kennedy, A.A. Kettrup, J.H. Koeman, H. Poiger, C. Rappe (1992). "Impact of polychlorinated dibenzo-p-dioxins, dibenzofurans, and biphenyls on human and environmental health, with special emphasis on application of the toxic equivalency factor concept." Eur J Pharmacol 228(4):179-99.

Ames, B.N., L.S. Gold, W.C. Willett (1995). "The causes and prevention of cancer." Proc Natl Acad Sci U S A 92(12):5258-65.

Ames, B.N., R. Magaw, L.S. Gold (1987). "Ranking possible carcinogenic hazards." Science 236(Apr):271-280.

ATSDR (1993). Toxicological Profile for Selected PCBs (Aroclor-1260, -1254, -1248, -1242, -1232, -1221, and -1016). Atlanta, GA, U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry 209.

Aylward, L.L., S.M. Hays, N.J. Karch, D.J. Paustenbach (1996). "Relative susceptibility of animals and humans to the cancer hazard posed by 2,3,7,8-tetrachlorodibenzo-p-dioxin using internal measures of dose." Environ Sci Technol 30:3534-3543.

Ayotte, P. (1996a). "Biomarkers of early biological responses induced by organochlorine exposure in women giving birth in Arctic Quebec." Environmental Studies, Northern Contaminants Program 73:309-312.

Ayotte, P., G. Carrier, E. Dewailly (1996b). "Health risk assessment for Inuit newborns exposed to dioxin-like compounds through breast feeding." Chemosphere 32(3):531-542.

Becker, P.R. (1993a). Alaska Marine Mammal Tissue Archival Project: Annual Report: U.S. DOC, National Marine Fisheries Service: Interagency Agreement No. 17909, Amendment No. 2.

Becker, P.R., B.J. Koster, S.A. Wise, R. Zeisler (1993b). "Biological Specimen Banking in Arctic Research: An Alaska Perspective." Science of the Total Environment 139/140:69-95.

Becker, P.R., E.A. Mackey, R. Demiralp, M.M. Schantz, B.J. Koster, S.A. Wise (1997a). "Concentrations of chlorinated hydrocarbons and trace elements in marine mammal tissues archived in the U.S. National Biomonitoring Specimen Bank." Chemosphere 34(9-10):2067-2098.

Becker, P.R., S.A. Wise, L. Thorsteinson, B.J. Koster, T. Rowles (1997b). "Specimen banking of marine organisms in the United States: current status and long-term prospective." Chemosphere 34(9/10): 1889-1906.

Bertazzi, P.A., A. Di Domenico (1994). "Chapter 18: Chemical, Environmental, and Health Aspects of the Seveso, Italy, Accident". Dioxins and Health, New York NY Plenum Press: 587-632.

Bertazzi, P.A., A.C. Pesatori, D. Consonni, A. Tironi, M.T. Landi, C. Zocchetti (1993). "Cancer incidence in a population accidentally exposed to 2,3,7,8-tetrachlorodibenzo-para-dioxin." Epidemiology 4:398-406.

Bertazzi, P.A., L. Riboldi, A. Pesatori, L. Radice, C. Zocchetti (1987). "Cancer mortality of capacitor manufacturing workers." American Journal of Industrial Medicine 11:165-176.

Birnbaum, L.S. (1994). "Endocrine effects of prenatal exposure to PCBs, dioxins, and other xenobiotics: implications for policy and future research." Environ Health Perspect 102:676-679.

Bowman, R.E., S.L. Schantz, S.A. Ferguson, H.Y. Tong, M. L. Gross (1990). "Controlled exposure of female rhesus monkeys to 2,3,7,8-TCDD; cognitive behavioral effects in their offspring." Chemosphere 20(7-9):1103-1108.

Bowman, R.E., S.L. Schantz, N.C.A. Weerasinghe, M.L. Gross, D.A. Barsotti (1989). "Chronic dietary intake of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) at 5 or 25 parts per trillion in the monkey: TCDD kinetics and dose-effect estimate of reproductive toxicity." Chemosphere 18(1-6):243-252.

Bromwich, P., J. Cohen, I. Stewart, A. Walker (1994). "Decline in sperm counts: An artefact of changed reference range of normal." Br Med J 309(Jul 2):19-22.

Brown, D.P. (1987). "Mortality of workers exposed to polychlorinated biphenyls - An update." Arch Environ Health 42:333-339.

Burkhard, L.P. (1987). "Determination of polychlorinated biphenyls using multiple regression with outlier detection and elimination." Anal Chem 59:1187-1190.

Burleson, G.R., H. Lebrec, Y.G. Yang, J.D. Ibanes, K.N. Pennington, L.S. Birnbaum (1996). "Effect of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) on influenza virus host resistence in mice." Fundam Appl Toxicol 29:40-47.

Carlsen, E., A. Giwercman, N. Keiding, N.E. Skakkeback (1992). "Evidence for the decreasing sperm quality of semen during the past 50 years." Br Med J 305:609-612.

Chan, L.H.M., O. Receveur, H.V. Kuhnlein (1996). "Assessment of effects of preparation on levels of organic contaminants in Inuit traditional food." Environmental Studies Northern Contaminants Program Centre for Nutrition and the Environment of Indigenous Peoples (CINE), McGill University 73:323-332.

Cheeke, P.R., L.R. Shull (1985). Natural Toxicants in Feeds and Poisonous Plants. Westport CT, AVI Publishing.

Chen, Y.-C.J., Y.-L. Guo, C.-C. Hsu, W.J. Rogan (1992). "Cognitive development of Yu-Cheng ('Oil Disease') children prenatally exposed to heat-degraded PCBs." J Am Med Assoc 268(22):3213-3218.

Colborn, T., D. Dumanoski, J.P. Myers (1996). Our Stolen Future Are We Threatening Our Fertility, Intelligence, and Survival? - A Scientific Detective Story. New York, Dutton 306.

Covello, V.T., M.W. Merkhofer (1993). Risk Assessment Methods Approaches for Assessing Health and Environmental Risks. New York, Plenum Press.

Crews, D., J.M. Bergeron, J.A. McLachlan (1995). "The role of estrogen in turtle sex determination and the effect of PCBs." Environ Health Perspect 103 (7):73-77.

De Swart, R.L., P.S. Ross, H.H. Timmerman, H.W. Vos, P.J.H. Reijnders, J.G. Vos, A.D. M. E. Osterhaus (1995). "Impaired cellular immune response in harbour seals (Phoca vitulina) feeding on environmentally contaminated herring." Clin Exp Immunol 101(May 9):480-486.

DeVito, M.J., L.S. Birnbaum (1994). "Chapter 5: Toxicology of Dioxins and Related Compounds". Dioxins and Health, New York NY Plenum Press: 139-162.

DeVito, M.J., L.S. Birnbaum, W.H. Farland, T.A. Gasiewicz (1995). "Comparisons of estimated human body burdens of dioxinlike chemicals and TCDD body burdens in experimentally exposed animals." Environ Health Perspect 103(9):820-831.

Dewailly, E., P. Ayotte, S. Bruneau, C. Laliberte, D.C.G. Muir, R.J. Norstrom (1993). "Inuit exposure to organochlorines through the aquatic food chain in arctic Quebec." Environ Health Perspect 101(7): 618-620.

Dewailly, E., A. Nantel, S. Bruneau, C. Laliberte, L. Ferron, S. Gingras (1992). "Breast milk contamination by PCDDs, PCDFs and PCBs in Arctic Quebec: a preliminary assessment." Chemosphere 25(7-10):1245-1249.

Dewailly, E., A. Nantel, J.-P. Weber, F. Meyer (1989). "High levels of PCBs in breast milk of Inuit women from Arctic Quebec." Bull Env Contam Tox 43:641-646.

Dewailly, E., J J. Ryan, C. Laliberte, S. Bruneau, J.-P. Weber, S. Gingras, G. Carrier (1994). "Exposure of remote maritime populations to coplanar PCBs." Environ Health Perspect 102(1):205-209.

Egeland, G.M., M.H. Sweeney, M.A. Fingerhut, K.K. Wille, T.M. Schnorr, W.E. Halperin (1994). "Total serum testosterone and gonadotropins in workers exposed to dioxin." Am J Epidemiol 139 (3):272-281.

Eroschenko, V.P. (1981). "Estrogenic activity of the insecticide chlordecone in the reproductive tract of birds and mammals." Toxicol Environ Health 8:731-742.

Falk, H. (1982). "Chapter 37: Liver". Cancer Epidemiology and Prevention, Philadelphia W. B. Saunders Company: 668-681.

Feeley, M.M. (1995). "Workshop on perinatal exposure to dioxin-like compounds. III. Endocrine effects." Environ Health Perspect 103(2):147-150.

Fein, G.G., J.L. Jacobson, S.W. Jacobson, P.M. Schwartz, J.K. Dowler (1984). "Prenatal exposure to polychlorinated biphenyls: Effects on birth size and gestational age." J Pediatr 105:315.

Fingerhut, M.A., W.E. Halperin, D.A. Marlow, L.A. Piacitelli, P.A. Honchar, M.H. Sweener, A.L. Greife, P.A. Dill, K. Steenland, A.J. Suruda (1991). "Cancer mortality in workers exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin." N Engl J Med 324 (Jan 24):212-218.

Fisch, H., E.T. Goluboff (1996). "Geographic variations in sperm counts: a potential cause of bias in studies of semen quality." Fertil Steril 65(6):1044-1046.

Ford, C.A., D.C.G. Muir, R.J. Norstrom, M. Simon, M.J. Mulvihill (1993). "Development of a semi-automated method for non-ortho PCBs: application to Canadian Arctic marine mammal tissues." Chemosphere 26(11):1981-1991.

Fraumeni, J.F., A. Kantor (1982). "Chapter 38: Biliary Tract". Cancer Epidemiology and Prevention, Philadelphia W. B. Saunders Company: 683-691.

Fraumeni, J.F.J., R.N. Hoover, S.S. Devesa, L.J. Kinlen (1993). "Chapter 9: Epidemiology of Cancer". Cancer: Principles & Practice of Oncology.4, Philadelphia J. B. Lippincott Co: 150-181.

Gangong, W.F. (1985). "The gonads: development & function of the reproductive system." Review of Medical Physiology: 342-347.

Giesy, J.P., D.J. Jude, D.E. Tillitt, R.W. Gale, J.C. Meadows, J.L. Zajieck, P.H. Peterman, D.A. Verbrugge, J.T. Sanderson, T.R. Schwartz, M.L. Tuchman (1997). "Polychlorinated dibenzo-p-dioxins, dibenzofurans, biphenyls and 2,3,7,8-tetrachlorodibenzo-p-dioxin equivalents in fishes from Saginaw Bay, Michigan." Environmental Toxicology and Chemistry 16(4): 713-724.

Giesy, J.P., D.A. Verbrugge, R.A. Othout, W.W. Bowerman, M.A. Mora, P.D. Jones, J.L. Newsted, C. Vandervoort, S.N. Heaton, R.J. Aulerich, S.J. Bursian, J.P. Ludwig, M. Ludwig, G.A. Dawson, T.J. Kubiak, D.A. Best, D.E. Tillitt (1994). "Contaminants in fishes from Great Lakes-influenced sections and above dams of three Michigan rivers. I: Concentrations of organo chlorine insecticides, polychlorinated biphenyls, dioxin equivalents, and mercury." Arch Environm Contam Toxicol 27:202-212.

Giwercman, A., E. Carlsen, N. Keiding, N.E. Skakkebaek (1993). "Evidence for increasing incidence of abnormalities of the human testis: a review." Environ Health Perspect 101(2):65-71.

Gladen, B.C., W.J. Rogan, P. Hardy, J. Thullen, J. Tingelstad, M. Tully (1988). "Development after exposure to polychlorinated biphenyls and dichlorodiphenyl dichloroethene transplacentally and through human milk." J Pediatr 113:991-995.

Golub, E.S., D.R. Green (1991). Immunology: A Synthesis. Sunderland MA, Sinauer Assoc Inc 744.

Gribble, G.W. (1994). "The natural production of chlorinated compounds." Environ Sci Technol 28(7):311-319.

Guillette, L.J.J. (1995). "Endocrine disrupting environmental contaminants and developmental abnormalities in embryos." Hum Ecol Risk Assess 1(2):25-36.

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Hall, A.J., R.J. Law, D.E. Wells, J. Harwood, H.M. Ross, S. Kennedy, C.R. Allchin, L.A. Campbell, P.P. Pomeroy (1992). "Organochlorine levels in common seals (Phoca vitulina) which were victims and survivors of the 1988 phocine distemper epizootic." Science of the Total Environment 115:145-162.

Hanson, D.J. (1991). "Dioxin toxicity: new studies prompt debate, regulatory action." C&EN (Aug 12):7-14.

Hardell, L., M. Eriksson, O. Axelson, S.H. Zahm (1994). "Chapter 16: Cancer Epidemiology". Dioxins and Health, New York NY Plenum Press: 525-548.

Harper, N., K. Connor, M. Steinberg, S. Safe (1995). "Immunosuppressive activity of polychlorinated biphenyl mixtures and congeners: Nonadditive (antagonistic) interactions." Fundam Appl Toxicol 27:131-139.

Hendricks, J.D., T.P. Putman, D.D. Bills, R.O. Sinnhuber (1977). "Inhibitory effect of a polychlorinated biphenyl (aroclor 1254) on aflatoxin B carcinogenesis in rainbow trout (Salmo gairdneri)." J Natl Cancer Inst 59(5):1545-1551.

Henriksen, G.L., J.E. Michalek, J.A. Swaby, A.J. Rahe (1996). "Serum dioxin, testosterone, and gonadotropins in veterans of Operation Ranch Hand." Epidemiology 7(4):352-357.

Herbst, A.L. (1981). "Clear cell adenocarcinoma and the current status of DES-exposed females." Cancer 48(Jul 15): 484-488.

Hofvander, Y. (1991). "Extent and Benefits of Breast-Feeding". Chemical Contaminants in Human Milk, Boca Raton CRC Press Inc: 1-8.

Hoover, A.A. (1988). "Steller Sea Lion - *Eumetopias jubatus*". Selected Marine Mammals of Alaska, Washington DC Marine Mammal Commmission: 159-194.

Hrutfiord, B.F., A.R. Negri (1992). "Dioxin sources and mechanisms during pulp bleaching." Chemosphere 25(1-2):53-56.

Hsu, C.-C., M.-L. Yu, Y.-C.J. Chen, Y.-L.L. Guo, W.J. Rogan (1994). "Chapter 20: The Yu-Cheng Rice Oil Poisoning Incident". Dioxins and Health, New York NY Plenum Press: 661-684.

Huisman, M., C. Koopman-Esseboom, V. Fidler, M. Hadders-Algra, C.G. Van der Paauw, L.G.M.T. Tuinstra, N. Weisglas-Kuperus, P.J.J. Sauer, B.C. L. Touwen, E.R. Boersma (1995). "Perinatal exposure to polychlorinated biphenyls and dioxins and its effect on neonatal neurological development." Early Human Development 41:111-127.

Humble, C.G., F.E. Speizer (1984). "Poly-brominated biphenyls and fetal mortality in Michigan." Am J Public Health 74(10):1130-1132.

Ilsen, A., J.M. Briet, J.G. Koppe, H.J. Pluim, J. Oosting (1996). "Signs of enhanced neuromotor maturation in children at 2 years and 7 months due to perinatal load with background levels of dioxins." Organohalogen Compounds 30:237-241.

Infante-Rivard, C., A. Fernandez (1993). "Otitis media in children: frequency, risk factors, and research avenues." Epidemiologic Reviews 15 (2):444-465.

IRIS (1996). IRIS Integrated Risk Information System. Denver CO, Micromedex Inc.

Jacobson, J.L., S.W. Jacobson (1996). "Intellectual impairment in children exposed to polychlorinated biphenyls in utero." N Engl J Med 335(11):783-789.

Jacobson, J.L., S.W. Jacobson, H.E.B. Humphrey (1990). "Effects of exposure to PCBs and related compounds on growth and activity in children." Neurotoxicol Teratol 12:319-326.

Jacobson, J.L., S.W. Jacobson, R.J. Padgett, G.A. Brumitt, R.L. Billings (1992). "Effects of prenatal PCB exposure on cognitive processing efficiency and sustained attention." Developmental Psychology 28 (2):297-306.

Jacobson, S.W., G.G. Fein, J.L. Jacobson, P.M. Schwartz, J.K. Dowler (1985). "The effect of intrauterine PCB exposure on visual recognition memory." Child Development 56:853-860.

Jensen, A.A. (1991a). "Levels and Trends of Environmental Chemicals in Human Milk". Chemical Contaminants in Human Milk, Boca Raton CRC Press Inc: 45-198.

Jensen, A.A., S.A. Slorach (1991b). "Overall Assessment and Evaluation". Chemical Contaminants in Human Milk, Boca Raton CRC Press Inc: 285-290.

Jensen, J., K. Akare, R. Shearer (1997). Canadian Arctic Contaminants: Indian and Northern Affairs Canada: Assessment Report QS-8525-000-EE-A1, Catalogue No R72-260/1997E, ISBN 0-662-25704-9.

Johansen, H.R., G. Becher, A. Polder, J.U. Skaare (1994). "Congener-specific determination of polychlorinated biphenyls and organochlorine pesticides in human milk from Norwegian mothers living in Oslo." Toxicol Environ Health 42:157-171.

Julien, G., J.D. Baxter, M. Crago, H.J. Ilecki, F. Therien (1987). "Chronic otitis media and hearing deficit among Native children of Kuujjuaraapik (Northern Quebec): a pilot project." Canadian Journal of Public Health 78(Jan/Feb):57-60.

Julshamn, K., A. Andersen, O. Ringdal, J. Morkore (1987). "Trace elements intake in the Faroe Islands. I. Element levels in edible parts of pilot whales *(Globicephalus meleanus)*." Science of the Total Environment 65:53-62.

Kannan, N., S. Tanabe, M. Ono, R. Tatsukawa (1989). "Critical evaluation of polychlorinated biphenyl toxicity in terrestrial and marine mammals: increasing impact of non-ortho and mono-ortho coplanar polychlorinated biphenyls from land to ocean." Arch Environm Contam Toxicol 18:850-857.

Kelley, D.S., P.A. Daudu (1993). "Fat intake and immune response." Prog Food Nutr Sci 17(1):41-63.

Kerkvliet, N.I. (1994). "Chapter 7: Immuno-toxicology of Dioxins and Related Chemicals". Dioxins and Health, New York NY Plenum Press: 199-226.

Kimbrough, R.D. (1980). Halogenated biphenyls, terphenyls, naphthalenes, dibenzodioxins and related products. Amsterdam, Elsevier North-Holland Biomedical Press 404.

Kimbrough, R.D. (1997). "Studies in children: polychlorinated biphenyls, dibenzo-p-dioxins and dibenzofurans." Health & Environment Digest 10(7):61-63.

Kinloch, D., H. Kuhnlein (1988). "Assessment of PCBs in Arctic foods and diets." Arct Med Res 47 (Suppl. 1):159-162.

Kinloch, D., H. Kuhnlein, D.C.G. Muir (1992). "Inuit foods and diet: a preliminary assessment of benefits and risks." Science of the Total Environment 122:247-278.

Kjeller, L.-O., K.C. Jones, A.E. Johnston, C. Rappe (1991). "Increases in the polychlorinated dibenzo-p-dioxin and -furan content of soils and vegetation since the 1840s." Environ Sci Technol 25(9):1619-1627.

Klinge, C.M., R.A. Bambara, R. Hilf (1992). "What differentiates antiestrogen-liganded vs estradiol-liganded estrogen receptor action?" Oncology Res 4 (4/5):137-144.

Knutsen, A.P. (1984). "Immunologic effects of TCDD exposure in humans." Bull Env Contam Tox 33:673-681.

Kociba, R.J., D.G. Keyes, J.E. Beyer, R.M. Carreon, C.E. Wade, D.A. Dittenber, R.P. Kalnins, L.E. Frauson, C. Parks, S.D. Darnard, R.A. Hummel, C.G. Humiston (1978). "Results of a two-year chronic toxicity and oncogenicity study of 2,3,7,8-tetrachlorodibenzo-p-dioxin in rats." Toxicol Appl Pharmacol 46:279-303.

Koopman-Esseboom, C., M. Huisman, N. Weisglas-Kuperus, C.G. Van der Paauw, L.G.M.T. Tuinstra, E.R. Boersma, P.J.J. Sauer (1994a). "PCB and dioxin levels in plasma and human milk of 418 Dutch women and their infants. Predictive value of PCB congener levels in maternal plasma for fetal and infant's exposure to PCBs and dioxins." Chemosphere 28(9):1721-1732.

Koopman-Esseboom, C., D.C. Morse, N. Weisglas-Kuperus, I.J. Lutkeschipholt, C.G. Van Der Paauw, L.G.M. Tuinstra, A. Brouwer, P.J.J. Sauer (1994b). "Effects of dioxins and polychlorinated biphenyls on thyroid hormone status of pregnant women and their infants." Pediatr Res 36(4):468-473.

Krahn, M.M., P.R. Becker, K.L. Tilbury, J.E. Stein (1997). "Organochlorine contaminants in blubber of four seal species: integrating biomonitoring and specimen banking." Chemosphere 34(9-10):2109-2121.

Krishnan, V., S. Safe (1993). "Polychlorinated biphenyls (PCBs), dibenzo-p-dioxins (PCDDs) and dibenzofurans (PCDFs) as antiestrogens in MCF-7 human breast cancer cells: quantitative structure-activity relationships." Toxicol Appl Pharmacol 120:55-61.

Kuhnlein, H.V. (1995a). "Benefits and risks of traditional food for indigenous peoples: focus on dietary intakes of Arctic men." Can J Physiol Pharmacol 73:765-771.

Kuhnlein, H.V., O. Receveur, D.C.G. Muir, H.M. Chan, R. Soueida (1995b). "Arctic indigenous women consume greater than acceptable levels of organochlorines." J Nutrition 125:2501-2510.

Kupfer, D., W.H. Bulger (1980). "Estrogenic properties of DDT and its analogs". Estrogens in the Environment, New York Elsevier/North-Holland: 239-262.

Landers, J.P.,N.J. Bunce (1991). "The Ah receptor and the mechanism of dioxin toxicity." Biochem J 276:273-287.

Lanier, A.P., L.R. Bulkow, B. Ireland (1989). "Cancer in Alaskan Indians, Eskimos, and Aleuts, 1969-83: implications for etiology and control." Public Health Reports: 658-664.

Lee, J.S., S. Tanabe, H. Umino, R. Tatsukawa, T.R. Loughlin, D.C. Calkins (1996). "Persistent organochlorines in Steller sea lion *(Eumetopias jubatus)* from the bulk of Alaska and the Bering Sea, 1976-1981." Mar Pollut Bull 32(7):535-542.

Levin, E.D., S.L. Schantz, R.E. Bowman (1988). "Delayed spatial alternation deficits resulting from perinatal PCB exposure in monkeys." Arch Toxicol 62:267-273.

Lipshultz, L.I. (1996). "The debate continues - the continuing debate over the possible decline in semen quality." Fertil Steril 65(5):909-911.

Lonky, E., J. Reihman, T. Darvill, J.S. Mather, H. Daly (1995). "Neonatal behavioral assessment scale performance in humans influenced by maternal consumption of environmentally contaminated Lake Ontario fish." J Great Lakes Res 22(2):198-212.

Loomis, W.F. (1986). "Chapter 12: Sex Differentiation". Developmental Biology, New York Collier Macmillan Publishers: 275-282.

Lowry, L.F., F.H. Fay (1984). "Seal eating by walruses in the Bering and Chukchi Seas." Polar Biol 3:11-18.

Lu, Y.-C., Y.-C. Wu (1985). "Clinical findings and immunological abnormalities in Yu-Cheng patients." Environ Health Perspect 59:17-29.

Luckas, B., W. Vetter, P. Fischer, G. Heidemann, J. Plotz (1990). "Characteristic chlorinated hydrocarbon patterns in the blubber of seals from different marine regions." Chemosphere 21(1-2):13-19.

Mably, T.A., D.L. Bjerke, R.W. Moore, A. Gendron-Fitspatrick, R.E. Peterson (1992a). "In utero and lactational exposure of male rats to 2,3,7,8-tetrachlorodibenzo-p-dioxin 3. Effects on spermatogenesis and reproductive capability." Toxicol Appl Pharmacol 114:118-126.

Mably, T.A., R.W. Moore, R.W. Goy, R.E. Peterson (1992b). "In utero and lactational exposure of male rats to 2,3,7,8-tetrachlorodibenzo-p-dioxin 2. Effects on sexual behavior and the regulation of luteinizing hormone secretion in adulthood." Toxicol Appl Pharmacol 114:108-117.

Mably, T.A., R.W. Moore, R.E. Peterson (1992c). "In utero and lactational exposure of male rats to 2,3,7,8-tetrachlorodibenzo-p-dioxin 1. Effects on androgenic status." Toxicol Appl Pharmacol 114:97-107.

Makura, S., H. Aoe, S. Sugihara, K. Hirao, M. Arai, N. Ito (1974). "Inhibitory effect of polychlorinated biphenyls on liver tumorigeneses in rats treated with 3'-methyl-4-dimethylaminoazo-benzene, N-2-fluorenylacetamide, and diethylnitrosamine." J Natl Cancer Inst 53 (5):1253-1257.

Masuda, Y. (1994). "Chapter 19: The Yusho Rice Oil Poisoning Incident". Dioxins and Health, New York NY Plenum Press: 633-660.

McFall, J.A., S.R. Antoine, E.B. Overton (1986). Organochlorine compounds and Polynuclear Aromatic Hydrocarbons In tissues of Subsistence Harvested Bowhead Whales, *Balaena mysticetus*: Center for Bio-Organic Studies, University of New Orleans: Final Report .

McFarland, V.A., J.U. Clarke (1989). "Environmental occurrence, abundance, and potential toxicity of polychlorinated biphenyl congeners: considerations for a congener-specific analysis." Environ Health Perspect **81**:225-239.

Mendola, P., G.M. Buck, J.E. Vena, M. Zielezny, L.E. Sever (1995). "Consumption of PCB-contaminated sport fish and risk of spontaneous fetal death." Environ Health Perspect **103**:498-502.

Middaugh, J.P., G.M. Egeland (1997). "Intellectual function of children exposed to polychlorinated biphenyls in utero." N Engl J Med **336**(9):660-661.

Miles, A.K., D.G. Calkins, N.C. Coon (1992). "Toxic Elements and Organochlorines in Harbor Seals (*Phoca vitulina richardsi*), Kodiak, Alaska, USA." Bull Environ Contam Toxicol **48**:727-732.

Morris, D.L., S.D. Jordan, M.P. Holsapple (1991). "Effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) on humoral immunity: I. Similarities to Staphylococcus aureus Cowan Strain I (SAC) in the in vitro T-dependent antibody response." Immunopharmacology **21**:159-170.

Muir, D. (1993a). "Spatial and Temporal Trends of Organochlorines in Arctic Marine Mammals". Synopsis of Research Conducted Under the 1992/93 Northern Contaminants Program.QS-8490-000-EF-A1 Catalogue No. R71-19/70-1993E ISBN 0-662-21037-9, Ottawa Browes, Pauline, Minister of Indian Affairs and Northern Development. **70**:88-94.

Muir, D. (1994a). "Spatial and temporal trends of organochlorines in arctic marine mammals." Environmental Studies, Northern Contaminants Program **72**:189-196.

Muir, D. (1996a). "Spatial and temporal trends of organochlorines in arctic marine mammals." Environmental Studies, Northern Contaminants Program **73**:143-146.

Muir, D., B. Grift, C. Ford, M. Segstro (1992a). "Circumpolar survey of PCBs in beluga." Environmental Studies, Northern Contaminants Program **68**:104-109.

Muir, D., B. Grift, C. Ford, M. Segstro (1992b). "Spatial trends in organochlorines in arctic ringed seal and walrus." Environmental Studies, Northern Contaminants Program **68**:73-76.

Muir, D., W.L. Lockhart (1993b). "Contaminant Trends in Freshwater Biota". Synopsis of Research Conducted Under the 1992/93 Northern Contaminants Program.QS-8490-000-EF-A1 Catalogue No. R71-19/70-1993E ISBN 0-662-21037-9, Ottawa Browes, Pauline; Minister of Indian Affairs and Northern Development. **70:**167-173.

Muir, D., W.L. Lockhart (1994b). "Contaminant trends in freshwater and marine fish." Environmental Studies, Northern Contaminants Program **72**:264-271.

Muir, D., W.L. Lockhart (1996b). "Contaminant trends in freshwater and marine fish." Environmental Studies, Northern Contaminants Program **73**:189-194.

Muir, D.C., R. Wagemann, B.T. Hargrave, D.J. Thomas, D.B. Peakall, R.J. Norstrom (1992c). "Arctic marine ecosystem contamination." Science of the Total Environment **122**(1-2):75-134.

Muir, D. C.G., C.A. Ford, R.E.A. Steward (1990). "Organochlorine contaminants in belugas, *Delphinapterus leucas*, from Canadian waters." Canadian Bulletin of Fisheries and Aquatic Sciences **224**:165-190.

Muir, D.C.G., R.J. Norstrom, M. Simon (1988). "Organochlorine contaminants in Arctic marine food chains: accumulation of specific polychlorinated biphenyls and chlordane-related compounds." Environ Sci Technol **22**(9):1071-1079.

Murray, J.L. (1992). Synopsis of Research Conducted Under the 1991-92 Northern Contaminants Program. Workshop in Support of the Technical and Science Managers Committees on Northern Ecosystems and Native Diets, Ottawa, Ontario, Tom Siddon, PC MP Minister of Indian Affairs and Northern Development. **68: **213.

Murray, J.L., R.G. Shearer (1993). Synopsis of Research Conducted Under the 1992/93 Northern Contaminants Program: Northern Affairs Program: Environmental Studies QS-8490-000-EF-A1 Catalogue No. R71-19/70-1993E ISBN 0-662-21037-9.

Murray, J.L., R.G. Shearer (1994). Synopsis of Research Conducted Under the 1993/94 Northern Contaminants Program: Hon. Ronald A. Irwin, P.C., M.P., Minister of Indian Affairs and Northern Development: Environmental Studies QS-8500-000-EF-A1 Catologue No. R71-19/72-1994E ISBN 0-662-22692-5.

Murray, J.L., R.G. Shearer, S.L. Han (1996). Synopsis of Research Conducted Under the 1994/95 Northern Contaminants Program: Hon. Ronald A. Irwin, P.C., M.P. Minister of Indian Affairs and Northern Development: Environmental Studies QS-8519-000-EF-A1 Catalogue No. R71-19/73-1995E ISBN 0-662+24414-1.

Nagayama, J., T. Ilda, H. Hirakawa, T. Matsueda, H. Tsuji, K. Okamura, M. Hasegawa, K. Sato, E. Kitahara, H.-Y. Ma, T. Yanagawa, I. Igarashi, J. l. Fukushigo, T. Watanabe (1996). "Effects of lactational exposure to chlorinated dioxins and related chemicals on lymphocyte subpopulations and thyroid function in Japanese babies". Organohalogen Compounds 30:228-233.

Nestrick, T.J., L.L. Lamparski (1982). "Isomer-specific determination of chlorinated dioxins for assessment of formation and potential environmental emission from wood combustion." Anal Chem 54 (13):2292-2299.

Neubert, R., G. Golor, R. Stahlmann, H. Helge, D. Neubert (1992). "Polyhalogenated dibenzo-p-dioxins and dibenzofurans and the immune system. 4. effects of multiple-dose treatment with 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) on peripheral lymphocyte subpopulations of a non-human primate (Callithrix jacchus)." Arch Toxicol 66:250-259.

Niimi, A.J., H.B. Lee, D.C.G. Muir (1996). "Environmental assessment and ecotoxicological implications of the co-elution of PCB congeners 132 and 153." Chemosphere 32(4):627-638.

Nobmann, E.D. (1989). Dietary Intakes of Alaska Native Adults 1987-1988: Alaska Area Native Health Service: Final.

Nobmann, E.D., T. Byers, A.P. Lanier, J H. Hankin, M.Y. Jackson (1992). "The diet of Alaska Native adults: 1987-1988." Am J Clin Nutr 55:1024-1032.

Norstrom, R.J., D.C.G. Muir (1994). "Chlorinated Hydrocarbon Contaminants in Arctic Marine Mammals." Science of the Total Environment 154 (2-3):107-128.

Norstrom, R.J., D.C.G. Muir, C.A. Ford, M. Simon, C.R. Macdonald, P. Beland (1992). "Indications of P450 Monooxygenase Activities in Beluga (Delphinapterus leucas) and Narwhal (Monodon monoceros) from Patterns of PCB, PCDD and PCDF Accumulation." Marine Environ Res 34:267-272.

Norstrom, R.J., M. Simon (1990). "Polychlorinated dibenzo-p-dioxins and dibenzofurans in marine mammals in the Canadian north." Environ Pollut 66:1-19.

Nutting, P.A., W.L. Freeman, D.R. Risser, S.D. Helgerson, R. Paisano, J. Hisnanick, S.K. Beaver, I. Peters, J.P. Carney, M.A. Speers (1993). "Cancer incidence among American Indians and Alaska Natives, 1980 through 1987." Am J Public Health 83 (11):1589-1598.

Oehme, M., S. Mano, B. Bjerke (1989). "Formation of polychlorinated dibenzofurans and dibenzo-p-dioxins by production processes for magnesium and refined nickel." Chemosphere 18(7-8):1379-1389.

Paulsen, C.A., N.G. Berman, C. Wang (1996). "Data from men in greater Seattle area reveals no downward trend in semen quality: further evidence that deterioration of semen quality is not geographically uniform." Fertil Steril 65(5):1015-1020.

Phillips, D.L., J.L. Pirkle, V.W. Burse, J.T.J. Bernert, L.O. Henderson, L.L. Needham (1989). "Chlorinated hydrocarbon levels in human serum: effects of fasting and feeding." Arch Environm Contam Toxicol 18:495-500.

Pitot, H.C., T. Goldsworthy, H.A. Campbell, A. Poland (1980). "Quantitative evaluation of the promotion by 2,3,7,8-tetrachlorodibenzo-p-dioxin of hepatocarcinogenesis from diethylnitrosamine." Cancer Res 40:3616-3620.

Pluim, H.J., J.J.M. De Vijlder, K. Olie, J.H. Kok, T. Vulsma, D.A. Van Tijn, J.W. Van der Slikke, J.G. Koppe (1993). "Effects of pre- and postnatal exposure to chlorinated dioxins and furans on human neonatal thyroid hormone concentrations." Environ Health Perspect 101(6):504-508.

Pocchiari, F., V. Silano, A. Zampieri (1979). "Human health effects from accidental release of tetrachlorodibenzo-p-dioxin (TCDD) at Seveso, Italy." Ann N Y Acad Sci 320: 311-320.

Poland, A., J.C. Knutson (1982). "2,3,7,8-Tetrachlorodibenzo-p-dioxin and related halogenated aromatic hydrocarbons: examination of the mechanism of toxicity." Ann Rev Pharmacol Toxicol 22:517-554.

Proulx, J.F. (1988). "Meningitis in Hudson's Bay, Northern Quebec, Canada." Arct Med Res 47 (1):686-687.

Rier, S.E., D.C. Martin, R.E. Bowman, W.P. Dmowski, J.L. Becker (1993). "Endometriosis in rhesus monkeys *(Macaca mulatta)* following chronic exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin." Fundam Appl Toxicol 21:433-441.

Rogan, W.J., B.C. Gladen (1991). "PCBs, DDE, and child development at 18 and 24 months." Ann Epidemiol 1:407-413.

Rogan, W.J., B.C. Gladen, J.D. McKinney, N. Carreras, P. Hardy, J. Thullen, J. Tinglestad, M. Tully (1986). "Neonatal effects of transplacental exposure to PCBs and DDE." J Pediatr 109 (Aug):335-341.

Ross, P.S., R.L. De Swart, H.H. Timmermann, P J.H. Reijnders, J.G. Vos, H. Van Loveren, A.D.M.E. Osterhaus (1996). "Suppression of natural killer cell activity in harbour seals *(Phoca vitulina)* fed Baltic Sea herring." Aquat Toxicol 34:71-84.

Rubin, C., A.P. Lanier, A. Harpster (1997). Environmental Chemicals and Health, Report of Pilot Study of Breast Cancer and Organochlorines in Alaska Native Women: CDC.

Safe, S. (1989). "Polychlorinated biphenyls (PCBs): mutagenicity and carcinogenicity." Mutation Res 220:31-47.

Safe, S. (1990). "Polychlorinated biphenyls (PCBs), dibenzo-p-dioxins (PCDDs), dibenzofurans (PCDFs), and related compounds: environmental and mechanistic considerations which support the development of toxic equivalency factors (TEFs)." Crit Rev Toxicol 21(1):51-88.

Safe, S., B. Astroff, M. Harris, T. Zacharewski, R. Dickerson, M. Romkes, L. Biegel (1991). "2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) and related compounds as antiestrogens: characterization and mechanism of action." Pharmacology & Toxicology 69:400-409.

Safe, S.H. (1994a). "Dietary and environmental estrogens and antiestrogens and their possible role in human disease." Environ Sci & Pollut Res 1(1):29-33.

Safe, S.H. (1994b). "Polychlorinated biphenyls (PCBs): environmental impact, biochemical and toxic responses, and implications for risk assessment." Crit Rev Toxicol 24(2):87-149.

Safe, S.H. (1995). "Environmental and dietary estrogens and human health: is there a problem?" Environ Health Perspect 103(4):346-51.

Sarokin, D., J. Schulkin (1992). "The role of pollution in large-scale population disturbances Part 1: Aquatic populations." Environ Sci Technol 25 (8):1476-1484.

Schantz, M.M., B.J. Koster, L.M. Oakley, S.B. Schiller, S.A. Wise (1995). "Certification of polychlorinated biphenyl congeners and chlorinated pesticides in a whale blubber standard reference material." Anal Chem 67(5):901-910.

Schantz, M.M., B.J. Koster, S.A. Wise, P.R. Becker (1993). "Determination of PCBs and Chlorinated Hydrocarbons in Marine Mammal Tissues." Science of the Total Environment 139/140:323-345.

Schantz, S.L., R.E. Bowman (1989a). "Learning in monkeys exposed perinatally to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD)." Neurotoxicol Teratol 11(1):13-19.

Schantz, S.L., E.D. Levin, R.E. Bowman, M.P. Heironimus, N.K. Laughlin (1989b). "Effects of perinatal PCB exposure on discrimination-reversal learning in monkeys." Neurotoxicol Teratol 11 (3):243-250.

Seegal, R.F., S.L. Schantz (1994a). "Chapter 13: Neurochemical and Behavioral Sequelae of Exposure to Dioxins and PCBs". Dioxins and Health, New York NY Plenum Press: 409-448.

Seegal, R.F., B. Bush, K.O. Brosch (1991). "Comparison of effects of Aroclors 1016 and 1260 on non-human primate catecholamine function." Toxicology **66**:145-163.

Seegal, R.F., B. Bush, K.O. Brosch (1994b). "Decreases in dopamine concentrations in adult, non-human primate brain persist following removal from polychlorinated biphenyls." Toxicology **86**:71-87.

Sheffield, A. (1985). "Sources and releases of PCDD's and PCDF's to the Canadian environment." Chemosphere **14**(6/7):811-814.

Shelton, D.W., D.E. Goeger, J.D. Hendricks, G.S. Bailey (1986). "Mechanisms of anti-carcinogenesis: the distribution and metabolism of aflatoxin B1 in rainbow trout fed Araclor 1254." Carcinogenesis **7**: 1065-1071.

Shu, H. P., D. J. Paustenbach,F. J. Murray (1987). "A critical evaluation of the use of mutagenesis, carcinogenesis, and tumor promotion data in a cancer risk assessment of 2,3,7,8-tetrachlorodibenzo-p-dioxin." Regul Toxicol Pharmacol **7**:57-58.

Silbergeld, E K., P.L. DeFur (1994). "Chapter 2: Risk Assessments of Dioxinlike Compounds". Dioxins and Health, New York NY Plenum Press: 51-78.

Silkworth, J.B., E.M. Grabstein (1982). "Polychlorinated biphenyl immunotoxicity: dependence on isomer planarity and the Ah gene complex." Toxicol Appl Pharmacol **65**:109-115.

Simmonds, M.P., P.A. Johnson, M.C. French, R. Reeve, J.D. Hutchinson (1994). "Organochlorines and mercury in pilot whale blubber consumed by Faroe islanders." Sci Tot Environ **149**:97-111.

Stehr, P.A., G. Stein, K. Webb, W. Schramm (1986). "A pilot epidemiologic study of possible health effects associated with 2,3,7,8-tetrachlorodibenzo-p-dioxin contaminations in Missouri." Archives of Environmental Health **41** (1):16-22.

Suskind, R.R. (1985). "Chloracne, "the hallmark of dioxin intoxication"." Scand J Work Environ Health **11**:165-171.

Svensson, B.G., T. Hallberg, A. Nilsson, A. Schutz, L. Hagmar (1994). "Parameters of immunological competence in subjects with high consumption of fish contaminated with persistent organochlorine compounds." Int Arch Occup Environ Health **65**:351-358.

Swart, R.d.L., P.S. Ross, L.J. Vedder, H.H. Timmerman, S. Heisterkamp, H. Van Loveren, J.G. Vos, P.J.H. Reijnders, A.D.M.E. Osterhaus (1994). "Impairment of immune function in harbor seals *(Phoca vitulina)* feeding on fish from polluted waters." Ambio **23**(2):155-159.

Sweeney, A. (1994). "Chapter 17: Reproductive Epidemiology of Dioxins". Dioxins and Health, New York NY Plenum Press: 549-586.

Tanabe, S., B.G. Loganathan, A. Subramanian, R. Tatsukawa (1987). "Organochlorine Residues in Short-Finned Pilot Whale: Possible Use as Tracers of Biological Parameters." Mar Pollut Bull **18** (10):561-563.

Tanabe, S., S. Watanabe, H. Kan, R. Tatsukawa (1988). "Capacity and mode of PCB metabolism in small cetaceans." Marine Mammal Science **4**(2):103-124.

Tarpley, R.J., T.L. Wade, E.M. Haubold (1994). Toxicological Studies in Tissues of the Beluga Whale *Delphinapterus leucas* along Northern Alaska with an Emphasis on Public Health Implications of Subsistence Utilization: Department of Veterinary Anatomy & Public Health Geochemical and Environmental Research Group Marine Mammal Research Program: Interim Report .

Tatematsu, M., K. Nakanishi, G. Murasaki, Y. Mlyata, M. Hirose, N. Ito (1979). "Enhancing effect of inducers of liver microsomal enzymes on induction of hyperplastic liver nodules by N-2-fluorenylacetamide in rats." J Natl Cancer Inst **63** (6):1411-1416.

Taylor, D.L., S. Schliebe, H. Metsker (1989). "Contaminants in blubber, liver, and kidney tissue of Pacific walruses." Mar Pollut Bull **20**(9):465-468.

Taylor, J.K. (1989b). Quality Assurance of Chemical Measurment. Chelsea MI, Lewis Publishers 328.

Taylor, P.R., C.E. Lawrence, H.-L. Hwang, A.S. Paulson (1984). "Polychlorinated biphenyls: influence on birthweight and gestation." Am J Public Health 74(10):1153-1154.

Theobald, M., R.E. Peterson (1994). "Chapter 10: Developmental and Reproductive Toxicity of Dioxins and Other Ah Receptor Agonists". Dioxins and Health, New York NY Plenum Press: 309-346.

Tong, H.Y., M.L. Gross, A. Schecter, S.J. Monson, A. Dekin (1990). "Sources of dioxins in the environment: second stage study of PCDD/Fs in ancient human tissue and environmental samples." Chemosphere 20(7-9):987-992.

Trosko, J.E., B. Dawson, C.-C. Chang (1981). "PBB inhibits metabolic cooperation in Chinese hamster cells in virto: its potential as a tumor promoter." Environ Health Perspect 37:179-182.

Tryphonas, H. (1994). "Immunotoxicity of polychlorinated biphenyls: present status and future considerations." Exp Clin Immunogenet 11(2-3):149-62.

USEPA (1994). Guidance For Assessing Chemical Contaminant Data For Use In Fish Advisories Volume II: Risk Assessment And Fish Consumption Limits: United States Environmental Protection Agency Office of Water: EPA 823-B-94-004.

USEPA (1995). Guidance For Assessing Chemical Contaminant Data For Use In Fish Advisories Volume 1: Sampling and Analysis, Second Edition: United States Environmental Protection Agency Office of Water (4305): EPA 823-R-95-007.

USEPA (1996). Guidance For Assessing Chemical Contaminant Data For Use In Fish Advisories Supplement to Volume II: Risk Assessment And Fish Consumption Limits: EPA Office Of Water (4305): EPA-823-B-96-004.

Usher, P.J., M. Baikie, M. Demmer, D. Nakashima, M.G. Stevenson, M. Stiles (1995). Communicating About Contaminants in Country Food: The Experience in Aboriginal Communities: Research Department Inuit Tapirisat of Canada: ISBN 0-9699774-0-9.

Varanasi, U., S.-L. Chan, B.B. McCain, J.T. Landahl, M.H. Schiewe, R.C. Clark, D.W. Brown, M.S. Myers, M.M. Krahn, W.D. Gronlund, W.D.J. MacLeod (1989). National Benthic Surveillance Project: Pacific Coast Part II Technical Presentation of the Results for Cycles I to III: Environmental Conservation Division Northwest Fisheries Center National Marine Fisheries Service National Oceanic and Atmospheric Administration: Technical Presentation.

Varanasi, U., J. Stein, E., K.L. Tilbury, D.W. Brown, J.P. Meador, M.M. Krahn, S.-L. Chan (1993). Contaminant Monitoring for NMFS Marine Mammal Health and Stranding Response Program. Coastal Zone 93: Proceedings of the 8th Symposium on Coastal and Ocean Management, New Orleans LA, ASCE:2516-2530.

Varanasi, U., J.E. Stein, K.L. Tilbury, J.P. Meador, C.A. Sloan, R.C. Clark, S. L. Chan (1994). "Chemical contaminants in gray whales *(Eschrichtius robustus)* stranded along the west coast of North America." Science of the Total Environment 145 (1-2):29-53.

Vuorinen, J.P., J. Paasivirta, J. Reistinen (1989). Comparison of the levels of organochlorines in Arctic and Baltic wildlife samples. 8th Int Conf Comite Artique Int on Global significance of the transport and accumulation of polychlorinated hydrocarbons, Oslo.

Wania, F., D. Mackay (1993). "Global fractionation and cold condensation of low volatility ogranochlorine compounds in polar regions." Ambio 22(1):10-18.

Watanabe, S., T. Shimada, S. Nakamura, N. Nishiyama, N. Yamashita, S. Tanabe, R. Tatsukawa (1989). "Specific profile of liver microsomal cytochorme P-450 in dolphin and whales." Marine Environ Res 27:51-65.

Webster, T., B. Commoner (1994). "Chapter 1: Overview: The Dioxin Debate". Dioxins and Health, New York NY Plenum Press: 1-50.

Weisglas-Kuperus, N., T.C.J. Sas, C. Koopman-Essenboom, C.W. Van der Zwan, M.A.J. De Ridder, A. Beishuizen, H. Hooijkaas, P.J.J. Sauer (1995). "Immunologic effects of background prenatal and postnatal exposure to dioxins and polychlorinated biphenyls in Dutch infants." Pediatr Res 38(3):404-410.

Williams, L.L., J.P. Giesy, N. DeGalan, D.A. Verbrugge, D.E. Tillitt, G.T. Ankley (1992). "Prediction of concentrations of 2,3,7,8-tetrachlorodibenzo-p-dioxin equivalents from total concentrations of polychlorinated biphenyls in fish fillets." Environ Sci Technol 26(6):1151-1159.

Wilson, R., S. Allen-Gil, D. Griffin, D. Landers (1995). "Organochlorine contaminants in fish from an Arctic lake in Alaska, USA." Science of the Total Environment 160/161:511-519.

Wolfe, W.H., J.E. Michalek, J.C. MIner, A.J. Rahe, C.A. Moore, L.L. Needham, D.G. Patterson (1995). "Paternal serum dioxin and reproductive outcomes among veterans of Operation Ranch Hand." Epidemiology 6(1):17-22.

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Surveillance and Research Needed for Public Health Policy

Increased community and scientific interest in the arctic environment during the past decade has led to identification of important monitoring and research needs. Many of these gaps in knowledge could be addressed through collaborative efforts that build upon partnerships that have developed between Alaska Natives, regional, state and federal public health agencies, and specialists in relevant scientific disciplines. Increased surveillance and research into the effects of global anthropogenic activities can lead to improved public health policies and wiser stewardship of the arctic ecosystem. Surveillance and research activities need to occur within the context of the cultural value of traditional foods. Thus, Alaska Native involvement and leadership is essential to the ongoing process of charting future research activities and in developing culturally appropriate communication messages.

Based on our evaluation of existing scientific evidence, we believe the following activities should be undertaken:

- Monitoring

    Increased systematic monitoring of heavy metals and PHDHs is needed to enable assessment of changing patterns and trends and to provide information for ongoing evaluation of the safety of subsistence food consumption.

    Monitoring of certain fish, marine, and terrestrial mammals needs to include systematic sampling so that an adequate number of specimens is obtained. Collection of specimens must include species high in the food chain, age, sex, parity, nutritional status, and geographic areas. Monitoring should include measuring concentrations of PHDHs in skin and blubber: and of heavy metals in kidney, liver, and muscle.

    Chemical analyses should measure specific chemical compounds including total mercury and methylmercury, cadmium, and selenium, and full analyses of PCB congeners including selected analyses of coplanar PCBs.

    Among the most important species to increase monitoring are the stellar sea lion and beluga whale.

- Baseline Comparison Levels

    To assist in understanding the magnitude and importance of anthropogenic pollution, monitoring selected species obtained in the relatively pristine Antarctic would be invaluable. Of particular importance would be determining levels of heavy metals and PHDHs in sea lion (to include total mercury and methylmercury, cadmium and selenium) and cadmium levels in penguins, including studies of the histopathology and metallothionein levels of kidney.

    To assist in understanding historical levels of exposure to heavy metals,

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analysis of archaeological remains of human and marine mammal hair for mercury, cadmium, and selenium would provide important information.

- Animal Studies

    Pharmacokinetic studies in laboratory animals could provide important evidence that would be invaluable in developing future public health guidelines. By experimentally feeding animals known amounts of marine mammal kidney and liver, measurements of concentrations of mercury, methylmercury, selenium, and cadmium in food and in tissues of animals fed experimentally could answer questions of absorption, distribution, metabolism, excretion, and pharmacokinetics.

- Human Studies

    Monitoring of maternal hair, blood, and breast milk could provide important data on trends of exposure to PHDHs and mercury, cadmium and selenium through minimally invasive procedures.

Field studies could focus on actual measurements of heavy metals and PHDHs in traditional foods and measurement of levels in persons consuming these foods.

Analysis of specimens of liver and kidney obtained at autopsy could establish body burdens of cadmium among individuals who have been highly exposed to traditional foods.

- Research on risk communication through development of culturally appropriate messages could improve use of existing information, increasing understanding of both scientists and consumers.

- Dietary surveys throughout Alaska will help identify nutritional deficiencies and be useful in promoting healthy eating habits, especially through educational programs targeting youth regarding the value of traditional foods.

- Additional research is needed on the nutrient value and health benefits of traditional foods.