

Consumption advisories for salmon based on risk of cancer and noncancer health effects [☆]

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Abstract

The levels of dioxins/furans, polychlorinated biphenyls (PCBs), and chlorinated pesticides were determined in farmed salmon for eight regions in Europe, North America, and South America, in salmon fillets purchased in 16 cities in Europe and North America, and in five species of wild Pacific salmon. Upon application of US Environmental Protection Agency (USEPA) methods for developing fish consumption advisories for cancer from mixtures of all of these substance for which USEPA has reported a cancer slope factor, the most stringent recommendation, for farmed salmon from northern Europe, was for consumption of at most one meal every 5 months in order to not exceed an elevated risk of cancer of more than 1 in 100,000. Farmed salmon from North and South America triggered advisories of between 0.4 and one meal per month. Retail market samples, in general, reflected levels found in regionally farmed fish, although much of the US salmon comes from Chile, which had somewhat lower contaminant levels than the North American farmed samples. Upon consideration of all of these organochlorine compounds as a mixture, even wild Pacific salmon triggered advisories of between one and less than five meals per month. The advisories are driven by the nondioxin-like PCBs and pesticides and not by dioxins/furans and coplanar PCBs. For noncancer effects for contaminants where USEPA has provided a reference dose only endrin and PCBs triggered any significant advisory. For both of these in the worst case, farmed salmon from northern Europe, the advice was not more than three meals per month.

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1. Introduction

In previous reports, we provided information on the concentrations of 14 organochlorine contaminants (Hites et al., 2004a) and 10 polybrominated diphenyl ether flame retardant congeners (Hites et al., 2004b) in farmed salmon

obtained from farms in eight major salmon farming regions of the world, samples of five species of wild Pacific salmon, and retail market samples of farmed salmon obtained in 16 cities in Europe and North America. We found that contaminant levels were about an order of magnitude higher in farmed and market samples than in wild Pacific salmon. Using this information, we also applied US Environmental Protection Agency (USEPA) advisory methods on frequency of consumption of fish based on prevention of greater than 1 in 100,000 risk of cancer for fish containing toxaphene, dieldrin, and polychlorinated biphenyls (PCBs) (Hites et al., 2004a), and we have applied

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advisory methods developed by both the USEPA and the World Health Organization (WHO) for dioxin-like compounds (Foran et al., 2005). In considering cancer risks only from PCBs, dieldrin, and toxaphene, use of the USEPA approach triggered very stringent advisories against frequent consumption. In the most extreme case, that of salmon obtained from farms in northern Europe, use of the USEPA method of calculation led to advice against consumption of farmed salmon more frequently than once every 4 months. Even the least contaminated farmed salmon, those from Chile, triggered advisories of not more than one or two meals per month.

However, salmon, whether farmed or wild, contain a variety of other contaminants that have not been considered in these consumption advisory calculations. Furthermore, we have not, to date, considered noncancer health effects. The USEPA has published consumption advisory methods for cancer and noncancer effects for a number of the contaminants that we have previously reported (Hites et al., 2004a) to be present in salmon. While it is the presence of PCBs, dieldrin, and toxaphene that dominate in the consumption advisories for salmon, other compounds present are also known to be carcinogenic and to have a variety of noncancer health effects. The purpose of this report is to apply these advisory methods to the full range of contaminants that we have measured in salmon obtained from farms in eight regions in Europe, North America, and South America, five species of wild Pacific salmon, and retail market samples of farmed salmon from 16 cities in Europe and North America.

The public health issues related to chemical mixtures are important for a variety of reasons. Persistent organic pollutants (POPs), which include PCBs, dioxins/furans and persistent pesticides, are fat-soluble substances that by virtue of their persistence in the environment are found in the fats of almost all living organisms (ATSDR, 2002). Food is usually the major route of exposure of humans to these contaminants. Travis and Hattemer-Frey (1991) estimated that 99% of human exposure to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) comes from food, and the other POPs are distributed in a similar fashion in animal fats. While the majority of health-directed research both in human populations and in laboratory experimental studies is directed at investigation of effects of single chemical substances, the reality is that each of us is exposed to a large mixture of different chemicals. Some, but not all, of these chemicals have common mechanisms of action (Carpenter et al., 2002). Furthermore, many, if not most, individual chemicals have actions at multiple sites. PCBs for example, are carcinogenic and immunosuppressive, disrupt thyroid and sex steroid function, are neurobehavioral toxicants, and act through a number of independent pathways (Carpenter, 1998). But PCBs are themselves a chemical mixture of up to a theoretical 209 distinct chemicals plus an unknown number of biologically active metabolites. Each of the individual congeners has its own profile of actions and different relative effects on liver

enzymes, immune system cells, neurons, thyroid transport proteins, sex hormone receptors, and gene induction (Hansen, 1999). Even the carcinogenicity of PCBs occurs via multiple pathways, some dependent upon activation of the aryl hydrocarbon receptor (AhR) (Safe, 1989) and others through AhR-independent mechanisms (Espandiar et al., 2003; van der Plas et al., 2000).

The USEPA risk assessment process is built around the assumptions that cancer risks are linearly related to dose and that relative cancer risk can be determined by knowledge of the cancer slope factor. With regard to carcinogenic substances in fish, USEPA (2000) presents formulas that indicate monthly rates of consumption of fish that will not elevate lifetime risk of cancer above 1 in 100,000. If two or more carcinogens are present and if the cancer slope factor for each is known, USEPA presents formulas for calculating frequency of consumption based upon consideration of all of the carcinogens present. These are the basis of the consumption advisory calculations for farmed salmon which we have previously presented (Hites et al., 2004a; Foran et al., 2005).

USEPA (2000) has developed a reference dose (RfD) for each chemical for noncancer effects. This RfD is defined as “an estimate (with uncertainty perhaps spanning an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime” (USEPA, 1987). They calculate the RfD by consideration of the no observed adverse effects level or the lowest observed adverse effects level with application of uncertainty and modifying factors. USEPA (2000) has a single advisory method for all noncancer effects, based primarily on the most sensitive endpoint, while acknowledging that there is less available information on some noncancer outcomes, such as immunotoxicity, neurotoxicity, and developmental toxicity.

There are several limitations and uncertainties with regard to these assumptions, especially for the noncancer effects. For noncancer effects there is the assumption that there is a “safe” level of exposure below which there will be no adverse effects. This assumption may or may not be correct. In addition the variety of noncancer outcomes for most contaminants is uncertain simply because of lack of information. Despite these uncertainties, the USEPA formulations provide the best available method for developing information on both cancer and noncancer health risks from fish consumption, and we have applied these formulations in this report for all of the chemicals that we have measured in salmon for which USEPA has published advisory methods.

2. Methods

The methods used have been previously described (Hites et al., 2004a,b; Foran et al., 2005) and will be only briefly summarized here. We purchased 459 whole farmed salmon from 51 farms in eight farming regions in six nations (Scotland, Norway, Faroe Islands, Eastern Canada,

Maine, Western Canada, Washington State, and Chile) and 135 wild Pacific salmon, including Chum, Coho, Chinook, Pink, and Sockeye, from suppliers in Alaska, British Columbia, and Oregon. In addition we purchased Atlantic salmon fillets in retail markets in 16 North American and European cities (Vancouver, Seattle, Los Angeles, San Francisco, Denver, Chicago, Toronto, New Orleans, Washington, DC, New York, Boston, London, Edinburgh, Paris, Frankfurt, and Oslo). All samples were obtained between September 2001 and December 2002.

All samples were analyzed by AXYS Analytical in Sidney, British Columbia. Fish were shipped to AXYS either fresh on icepacks or frozen. After thawing and inspection by a fisheries biologist to verify the species, fish were weighed and filleted to give two skin-on fillets. Composites were made of fillets from three fish from the same farm or region or three fillets from the same retail market.

USEPA methods were used in all analyses, based on gas chromatographic high-resolution mass spectrometry (GC/HRMS) with isotopically labeled internal standards. Dioxins and furans were determined using USEPA Method 1613 and reported as the content of seven toxic dioxin and 10 toxic furan congeners, plus total tetra-, penta-, hexa-, and hepta-dioxins and furans. In addition, total toxic equivalents (TEQs), assuming nondetects to be zero (to be conservative and because of the very low

detection limits) and using WHO toxic equivalent factors, were reported. PCBs were measured using USEPA Method 1668A, an isotope-dilution, congener-specific method for the 12 dioxin-like congeners and an internal standard for all of the remaining 197 congeners. The dioxin-like congeners were reported as TEQs assuming that nondetects were zero and using WHO toxic equivalent factors. The organopesticides were determined using a GC/HRMS isotope dilution method analogous to the USEPA methods used for dioxins and PCBs. Toxaphene was measured by GCMS using the electron capture negative ion mode. Total toxaphene was determined using ¹³C-labeled PCB-180 as an internal standard, with Hercules toxaphene as a reference. ¹³C-dieldrin was used for quantification of dieldrin.

The QA/QC methods used are detailed in the report of Hites et al. (2004a). In brief, each analysis included a procedural blank, a laboratory control sample, and an analysis duplicate, and results were evaluated against the method criteria to ensure quality. Reported concentrations were adjusted for the recoveries of the internal standards. All blank measurements were at or near the detection limits and therefore were not subtracted.

Table 1 lists the ranking of each of the contaminants that we have measured with regard to carcinogenicity by the USEPA (2000) and International Agency for Research on Cancer (IARC, 2004), an agency of the WHO. With a few minor exceptions both are in general agreement that these are carcinogenic substances, documented in animal studies and likely in humans (listed as “probable” by USEPA terms, “possible” by IARC). The cancer slope factors used by USEPA are also shown in Table 1.

Table 2 lists the variety of noncancer effects of these contaminants as derived from the information on IRIS (1999), USEPA (2000), and the IARC website (2004) and several of the ATSDR Toxicological Profiles (1994, 1996). USEPA (2000) has also presented risk-based consumption limit recommendations based on consideration of noncancer health effects for total chlordane, total dichlorodiphenyltrichloroethane (DDT), dieldrin, endrin, heptachlor epoxide, hexachlorobenzene, lindane, mirex, toxaphene, and PCBs. Table 2 also gives the RfD used by USEPA (2000).

We applied the methodology developed by USEPA (2000) to derive advisory consumption recommendations for multiple carcinogens in fish, based on the cancer slope factor for each compound and calculated to prevent 1 excess cancer in 100,000 over lifetime exposure,

$$CR_{lim} = \frac{(ARL)(BW)}{\sum_{m=1}^X C_m(CSF_m)}, \tag{1}$$

where CR_{lim} is the maximum allowable fish consumption rate (kg/day), ARL the maximum acceptable lifetime risk level (unit-less), BW the consumer body weight (kg), X the number of contaminants, C_m the measured concentration of contaminant m in a given species of fish (mg/kg), and CSF_m is the cancer slope factor for contaminant m, usually the

Table 1
Carcinogenicity as classified by USEPA and IARC for chlorinated pesticides, PCBs, and dioxins

	EPA		IARC	
	Rank ^a	CSF ^b	Animals	Humans
Chlordane	B2	0.35	Sufficient	Possible
DDT, DDE, DDD	B2	0.34	Sufficient	Possible
Dieldrin	B2	16	Inadequate	Not classifiable
Endrin	D	—	Inadequate	Not classifiable
Heptachlor epoxide	B2	9.1	Sufficient	Possible
Hexachlorobenzene	B2	1.6	Sufficient	Possible
Lindane	B2/C	1.3	Sufficient	Possible
Mirex	B2	?	Sufficient	Possible
Toxaphene	B2	1.1	Sufficient	Possible
PCBs	B2	0.7–2	Sufficient	Probable
Dioxin	B1/B2	1.56 × 10 ⁵	Sufficient	Sufficient

^aB1, sufficient; B2, probable based on animal studies; C, possible; D, not classifiable.

^bCancer slope factor in mg/kg d.

Table 2
Noncancer effects of chlorinated pesticides, PCBs, and dioxins

Contaminant RfD (mg/kg-d)	Immune suppression	IQ/CNS	Feto-tox	Repro	Musculo skeletal	Liver	Kidney	CV/blood	Endocrine dys
Chlordane (5 × 10 ⁻⁴)	X	X				X		X	X
DDT/DDE (5 × 10 ⁻⁴)	X	X	X	X		X		X	X
Dieldrin (5 × 10 ⁻⁵)	X	X	X	X	X	X	X	X	X
Dioxin (—)	X	X	X	X	X	X		X	X
Endrin (3 × 10 ⁻⁴)		X		X	X				X
HCB (8 × 10 ⁻⁴)	X	X	X		X	X	X	X	X
Heptachlor (1.3 × 10 ⁻⁵)		X		X	X	X		X	
Lindane (3 × 10 ⁻⁴)	X	X	X	X		X	X		
Mirex (2 × 120 ⁻⁴)			X	X		X	X	X	X
PCBs (2 × 10 ⁻⁵)	X	X	X	X	X	X	X	X	X
Toxaphene (2.5 × 10 ⁻⁴)	X	X				X	X		X

IQ/CNS, decrements in IQ and/or central nervous system effects; Feto-tox, fetotoxicity; Repro, reproductive effects; CV/blood, cardiovascular or hematological effects; Endocrine dys, endocrine dysfunction.

upper 95% confidence limit on the linear term in the multistage model used by USEPA (mg/kg d).

For noncancer endpoints for single contaminants based on the RfD,

$$CR_{\text{lim}} = \frac{(\text{RfD})(\text{BW})}{C_m}, \quad (2)$$

where CR_{lim} is the maximum allowable fish consumption rate (kg/day), RfD the reference dose (mg/kg d), BW the consumer body weight (kg), and C_m is the measured concentration of chemical contaminant m in a given species of fish (mg/kg). The CR_{lim} for multiple contaminants assumes that effects are additive. Both of the approaches assume that meal size is 8 oz. USEPA (2000) notes that Eq. (2) cannot be applied when there are different noncancer endpoints.

In our previous report we compared contaminant concentrations using a one-way analysis of variance (ANOVA) (Hites et al., 2004a). In this analysis we applied a two-way ANOVA (Der and Everitt, 2002; Kleinbaum et al., 1998) to compare salmon from different sources and regions. Planned comparison contrasts were used to test the difference in contaminant concentrations based on source and region. We have also performed multiple pairwise comparisons to determine the degree to which levels of the various contaminants were correlated.

3. Results

Fig. 1 shows the concentrations of PCBs and dioxins expressed as total concentrations and independently as TEQs for farmed, market, and wild salmon. As previously reported (Hites et al., 2004a), levels for both PCBs and dioxins were significantly higher in farmed and market samples than in wild Pacific salmon. Levels in both the farmed and the retail market samples from northern Europe were much higher than most of those from North America, while levels in farmed salmon from Chile were the lowest. These regional differences are probably a result of differences in the contaminant content in the fish meal/fish oil that is fed to the farmed salmon, as we have previously reported (Hites et al., 2004a). Since 83% of the farmed salmon filets imported and sold in the US in 2003 came from Chile, and since the US production of farmed salmon is relatively small (Harvey, 2004), some but not all of the US retail market samples are similar to the Chilean farmed fish.

Several findings are of note. The overall pattern of content of dioxins and PCBs is similar. More than two-thirds of the total TEQ comes from PCBs and not dioxins. However, the pattern of concentration of TCDD is different from that observed for total PCBs, total dioxins/furans, or total dioxin TEQs, with relatively higher concentrations found in samples obtained from Western Canada and Chile, and from retail markets in San Francisco and Los Angeles. This may reflect regional ambient levels or a local source.

Figs. 2 and 3 show concentrations of various pesticides in the farmed, retail market, and wild salmon. While the difference between the farmed and the wild fish is not as striking as is the case for dioxins and PCBs, the general pattern applies to almost all contaminants. Seven of those contaminants were significantly more concentrated in the farmed salmon as a group than in the wild salmon [$P = 0.056$ for hexachlorobenzene (HCB); $P = 0.0113$ for

endrin; and $P < 0.01$ for the other six contaminants]. When the concentrations of all measured pesticides were added, total pesticide levels were significantly higher in farmed than in wild salmon.

Table 3 shows the results of a two-way ANOVA of contaminant concentrations in salmon based on different sources and regions. The overall ANOVA model is highly significant ($P < 0.0001$) for all eight contaminants and total pesticides. Salmon from Europe had significantly higher contaminant levels than those from North America for seven of these organochlorine compounds (all except $P = 0.8175$ for lindane, whose level in European and North American salmon were about the same). Salmon from South America had significantly lower contaminant levels than those from North America for seven compounds (all except $P = 0.7695$ for mirex, whose levels in South American and North American salmon were about the same). For all pesticides, the salmon from northern Europe were more contaminated than those from North America, while salmon from South America had the least contamination. Farmed salmon had significantly higher contaminant levels than wild salmon for all contaminants except HCB ($P = 0.056$). The results also showed that, generally, farmed salmon were the most contaminated; salmon purchased from supermarkets were less contaminated (most likely due to overrepresentation of Chilean salmon from supermarkets in US cities), and wild salmon were the least contaminated.

Fig. 4 is a grid of scatter plots for each pair of contaminants. We observed clear patterns of positive correlation for all pairs of contaminants with one exception. Table 4 lists correlation coefficients and P values for each pair of contaminants. Other than the pair lindane and mirex, the concentrations of all pairs of contaminants were strongly positively correlated, and the correlations were highly significant (all P values < 0.0001 for pairs not including lindane). Lindane had lower but still positive correlations that were highly significant (all P values < 0.01) with all other contaminants except mirex.

We have previously published consumption levels based upon USEPA advisory methods considering the concentrations of PCBs, toxaphene, and dieldrin (Hites et al., 2004a) and total dioxin TEQs (Foran et al., 2005). Fig. 5 shows a similar calculation based on cancer risk for the mixture of all of the contaminants that we found in salmon for which USEPA (2000) has provided cancer risk estimates based on cancer slope factors [PCBs, dioxin, dieldrin, toxaphene, total chlordane (sum of *cis*- and *trans*-chlordane, *cis*- and *trans*-nonachlor, and oxychlordane), total DDT (sum of 4,4'- and 2,4'-isomers of DDT, dichlorodiphenyldichloroethylene (DDE), and dichlorodiphenyldichloroethane (DDD)), heptachlor epoxide, HCB, and lindane]. The most restrictive advisory in this analysis changes only slightly to one meal every 5 months when considering all of the contaminants for which USEPA provides calculation methods from the one meal every 4 months that was determined for northern European

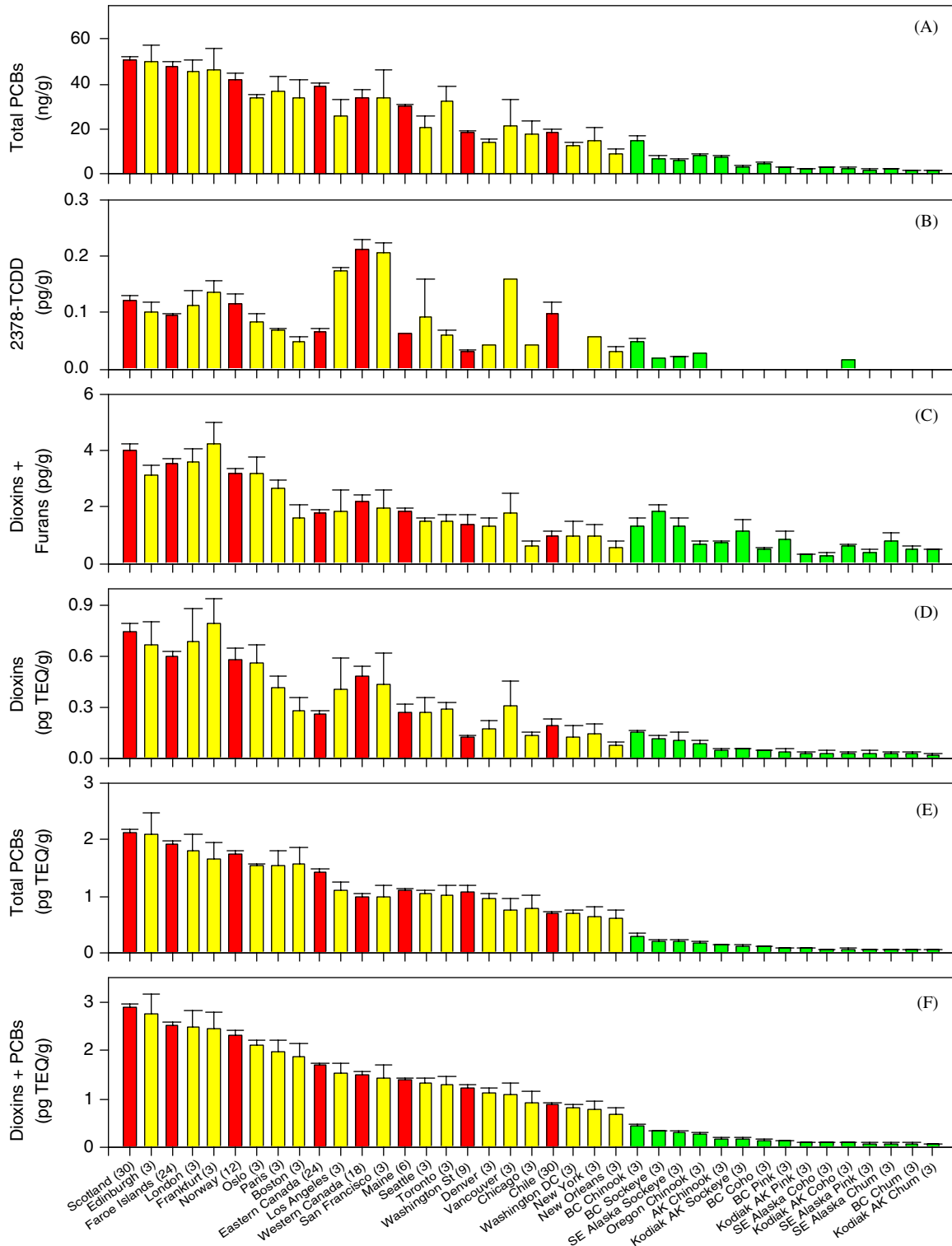


Fig. 1. PCB and dioxin/furan concentrations in farmed (red), retail market (yellow), and wild (green) salmon from different countries and cities. (A) Total PCB concentrations (ng/g wet weight). (B) Concentrations (pg/g wet weight) of 2,3,7,8-tetrachloro dibenzo-*p*-dioxin (TCDD). (C) Total concentration (pg/g wet weight) of 17 dioxin and furan congeners. (D, E, and F) WHO TEQs (pg/g wet weight) for dioxins/furans, total PCBs, and total dioxins/furans plus total PCBs, respectively. The error bars are standard errors, and the number of samples analyzed is shown in parentheses after the origin of the sample. The locations are sequenced from highest to lowest total dioxins plus PCB TEQs.

farmed salmon on consideration of only PCBs, dieldrin, and toxaphene. However, the other advisory calculations are more restrictive, including those for the wild salmon. It

is important to emphasize that it is the nondioxin-like PCBs and the pesticides, especially dieldrin and toxaphene, that drive these advisories and not dioxin TEQs.

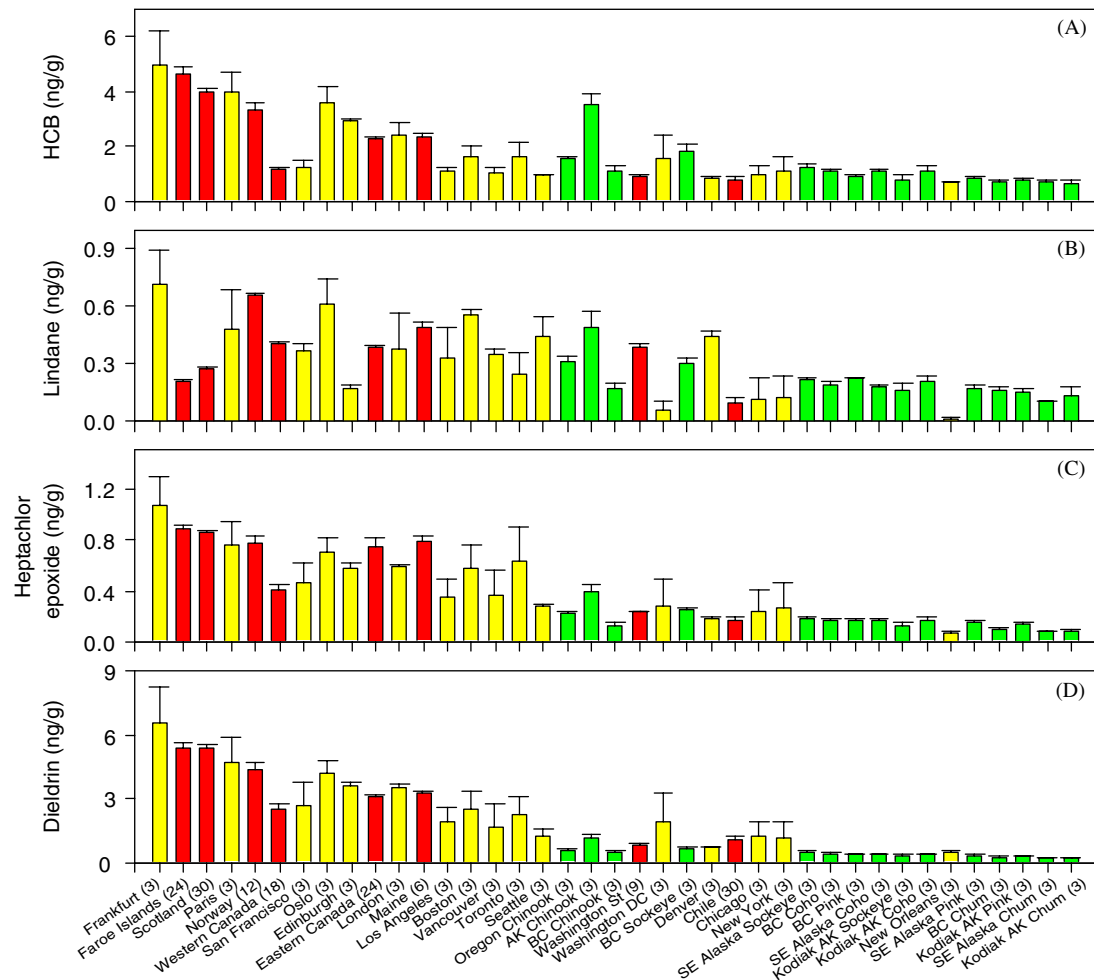


Fig. 2. Concentrations of hexachlorobenzene (HCB) (A), lindane (B), heptachlor epoxide (C), and dieldrin (D), all expressed as ng/g wet weight, in farmed (red), retail market (yellow), and wild (green) salmon from various countries and cities. The error bars represent standard errors. The number of samples is given in parentheses after the location. Samples are sequenced on the basis of highest to lowest total pesticide levels (see Fig. 3).

Fig. 6 shows the result for noncancer health effects for endrin, while Fig. 7 shows similar results for PCBs, these being the contaminants that trigger the most restrictive consumption levels. For the most contaminated fish, both endrin and PCBs trigger noncancer consumption rates of four meals per month. Farmed salmon from Washington State and Chile did not differ much from wild salmon in terms of concentration of endrin, but other sources of farmed salmon for endrin and all farmed salmon for PCBs trigger much more restrictive consumption rates than those for wild Pacific salmon. Mirex and toxaphene were the only other contaminants that triggered any significant consumption recommendations for non-cancer effects, the most stringent being 11 and 13 meals per month, respectively, for the farmed salmon from the Faroe Islands, while for the wild salmon the most stringent consumption for mirex was 31 meals per month for one sample of British Columbia sockeye and 47 meals per month for toxaphene in one sample of Alaska chinook.

4. Discussion

Perhaps our most striking observation is the finding that if a fish sample is high in one of the contaminants measured, it is similarly high in all of the others, with the partial exception of lindane. Since 13 of the 14 contaminants that we have reported are either known or probable human carcinogens, and since all of them have a variety of noncancer actions, clearly if one hopes to protect against risks of cancer, noncancer effects, or both, one must deal with the fact that fish contain a chemical mixture of contaminants. Unfortunately we have few well-developed and validated tools for evaluating health risks of chemical mixtures and inadequate information on the degree and nature of interactions among the various contaminants (see ATSDR, 2002).

Most of the contaminants in farmed salmon are rated as “probable” (by USEPA) or “possible” (by IARC) human carcinogens. These qualified ratings for humans are a result of demonstration of carcinogenicity in animal experiments

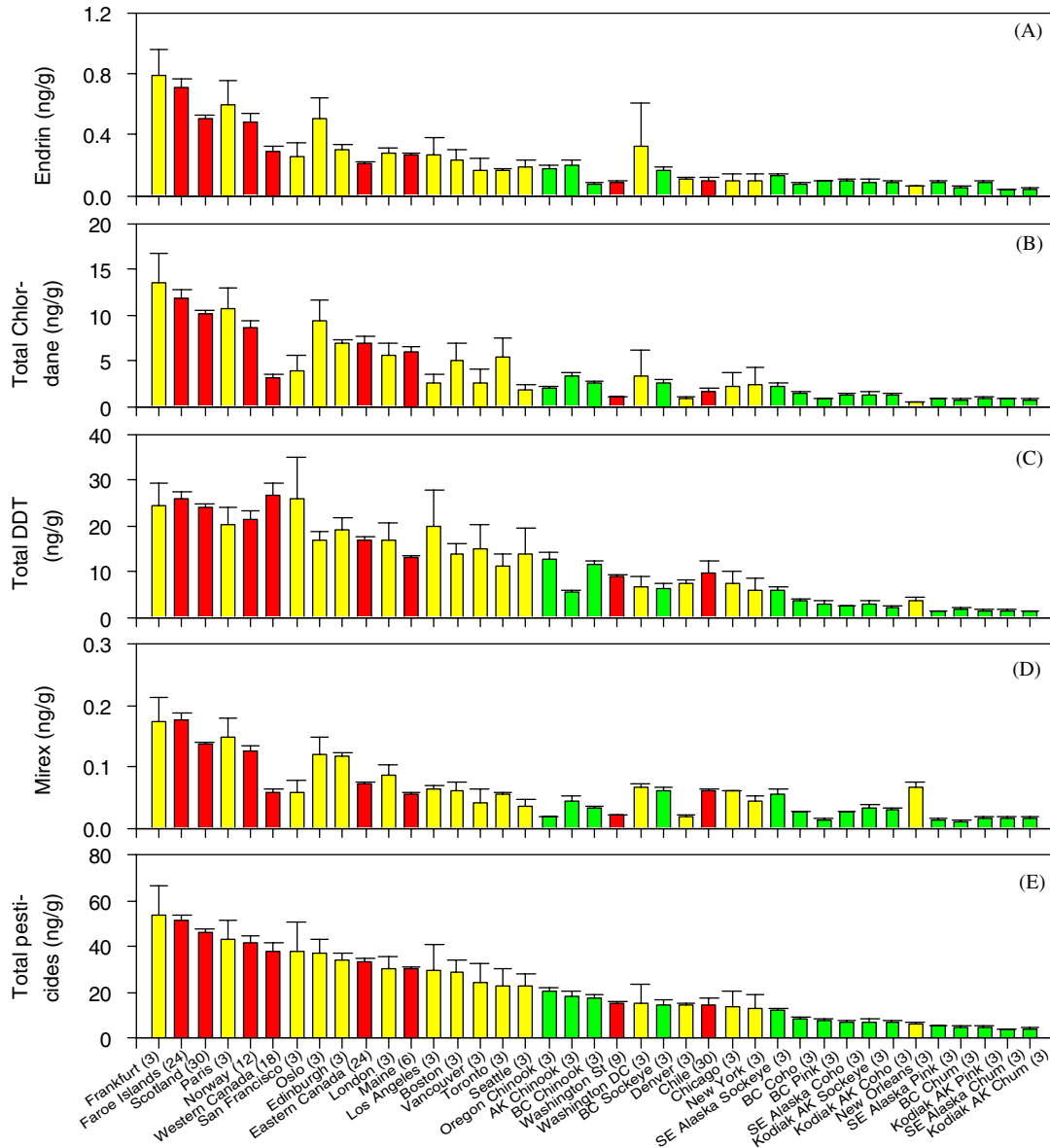


Fig. 3. Concentrations of endrin (A), total chlordane (includes sum of oxychlordane, gamma-chlordane, alpha-chlordane, *trans*-nonachlor, and *cis*-nonachlor) (B), total DDT (includes sum of 4,4'- and 2,4'-isomers of DDT, DDE, and DDD) (C), mirex (D), and total pesticides [includes sum of hexachlorobenzene, total hexachlorocyclohexane (sum of alpha, beta and gamma hexachlorocyclohexane), heptachlor, aldrin, octachlorostyrene, heptachlor epoxide, dieldrin, endrin, endrin ketone, total chlordane, total DDT, mirex, alpha-endosulfan, beta-endosulfan, endosulfan sulfate, and methoxychlor] (all in ng/g wet weight) in farmed (red), retail market (yellow), and wild (green) salmon from various countries and cities (E). Samples are sequenced on the basis of highest to lowest total pesticide concentrations.

but less information from human studies. The major reason for lack of proof in human studies is that, other than in occupational settings where the exposed population is usually small, these fat-soluble compounds usually exist together. Therefore determining with confidence that a particular cancer was caused by toxaphene rather than by dieldrin or one of the other lipophilic substances is difficult. However, given the similarity in genetic composition between humans and other animals, it is unlikely that animal carcinogens are not also human carcinogens, at least at some dose.

The difficulties are even greater for noncancer health effects than for cancer. Contaminants may affect various

organ systems and often do so by independent mechanisms (Carpenter et al., 2002). Many of these substances have not been studied using contemporary methods for investigation of immunologic, neurobehavioral, and developmental toxicities, in part because they have not been manufactured for many years and there is a perception that, since overall levels are going down, they no longer constitute a problem. However, our knowledge of the dangers of some of these compounds has grown faster than the levels have declined. Subtle alterations in resistance to infections or small decrements in intelligence and attention span may in fact be more serious impacts from a societal point of view than small increases in risks of cancer, particularly in the case

Table 3
Comparison of contaminant concentrations in salmon from three sources produced in three continents, showing F statistics and P values from the two-way analysis of variance

	HCB	Lindane	Heptachlor epoxide	Dieldrin	Endrin	Total chlordane	Total DDT	Mirex	Total pesticide
<i>Overall ANOVA result</i>									
<i>F</i>	56.91	7.44	39.56	75.25	38.92	40.58	16.85	45.57	33.59
<i>P</i> value	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
<i>Planned comparison I: region</i>									
	E>N>S	E = N>S	E>N>S	E>N>S	E>N>S	E>N>S	E>N>S	E>N = S	E>N>S
<i>Planned comparison contrast: Europe vs. North America</i>									
<i>F</i>	127.26	0.05	39.15	112.84	79.43	72.07	8.55	109.74	29.91
<i>P</i> value	<0.0001	0.8175	<0.0001	<0.0001	<0.0001	<0.0001	0.0045	<0.0001	<0.0001
<i>Planned comparison contrast: Europe vs. South America</i>									
<i>F</i>	126.38	20.29	89.32	138.92	82.44	83.84	24.13	52.99	63.72
<i>P</i> value	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
<i>Planned comparison contrast: North America vs. South America</i>									
<i>F</i>	9.14	21.02	25.66	16.2	6.67	8.75	7.53	0.09	15.61
<i>P</i> value	0.0034	<0.0001	<0.0001	0.0001	0.0117	0.0041	0.0075	0.7695	0.0002
<i>Planned comparison II: source</i>									
	F>SM = W	F>SM>W	F>SM>W	F>SM>W	F>SM>W	F>SM>W	F>SM>W	F = SM>W	F>SM>W
<i>Planned comparison contrast: farmed vs. wild</i>									
<i>F</i>	3.77	8.59	34.11	41.58	6.74	12.63	27.1	8.22	34.02
<i>P</i> value	0.056	0.0045	<0.0001	<0.0001	0.0113	0.0007	<0.0001	0.0053	<0.0001
<i>Planned comparison contrast: supermarket vs. wild</i>									
<i>F</i>	0.02	5.41	7.77	12.15	1.37	2.14	7.57	3.64	8.55
<i>P</i> value	0.8918	0.0226	0.0067	0.0008	0.2461	0.1472	0.0074	0.06	0.0045
<i>Planned comparison contrast: farmed vs. supermarket</i>									
<i>F</i>	5.42	0.16	9.48	8.41	2.12	4.66	5.84	0.72	8.44
<i>P</i> value	0.226	0.6857	0.0029	0.0049	0.1495	0.034	0.018	0.3989	0.0048

E, Europe; N, North America; S, South America; F, farmed salmon; SM, supermarket salmon; W, wild salmon.

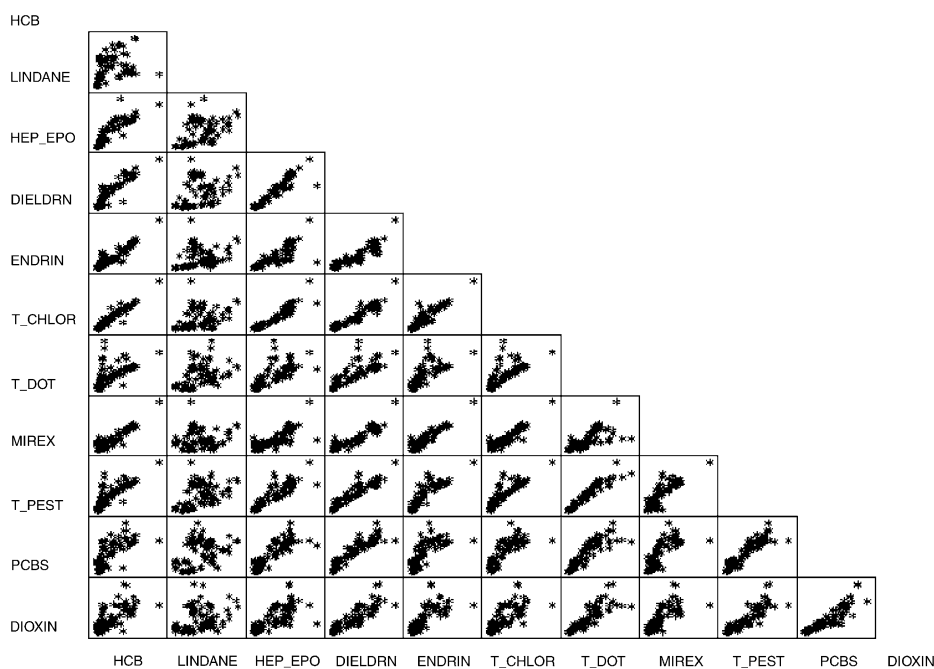


Fig. 4. Scatter-plot matrix for the content of pairs of 10 contaminants and total pesticides measured in salmon samples from various locations where the salmon were produced or purchased. HEP_EPO, heptachlor; T_CHLOR, total chlordane; T_DDT, total DDT; T_PEST, total pesticide.

Table 4
Correlation matrix for levels of 10 contaminants and total pesticides among the various salmon samples analyzed

HCB											
Lindane	0.2936										
	0.0074										
Heptachlor epoxide	0.8761	0.4590									
	<0.0001	<0.0001									
Dieldrin	0.9145	0.3586	0.9333								
	<0.0001	0.0009	<0.0001								
Endrin	0.9219	0.2972	0.8071	0.9109							
	<0.0001	0.0067	<0.0001	<0.0001							
Total chlordane	0.9581	0.3124	0.9351	0.9465	0.9141						
	<0.0001	0.0043	<0.0001	<0.0001	<0.0001						
Total DDT	0.6050	0.3831	0.7183	0.8041	0.7141	0.6932					
	<0.0001	0.0004	<0.0001	<0.0001	<0.0001	<0.0001					
Mirex	0.9074	0.1250	0.7782	0.8949	0.9272	0.9156	0.6807				
	<0.0001	0.2631	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001				
Total pesticide	0.8118	0.4361	0.8822	0.9355	0.8609	0.8779	0.9488	0.8218			
	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001			
Total PCBs	0.7260	0.3514	0.8493	0.9121	0.7241	0.8020	0.8684	0.7467	0.9128		
	<0.0001	0.0012	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001		
Dioxin	0.6965	0.3038	0.7281	0.8711	0.7458	0.7334	0.8509	0.7468	0.8691	0.8983	
	<0.0001	0.0055	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	
	HCB	Lindane	Heptachlor epoxide	Dieldrin	Endrin	Total chlordane	Total DDT	Mirex	Total pesticide	Total PCBs	Dioxin

For each cell, the upper part is the correlation coefficient for the pair of variables; the lower part is the *P*value associated with the test of zero correlation. Small *P* values indicate a strong non-zero correlation between the two variables.

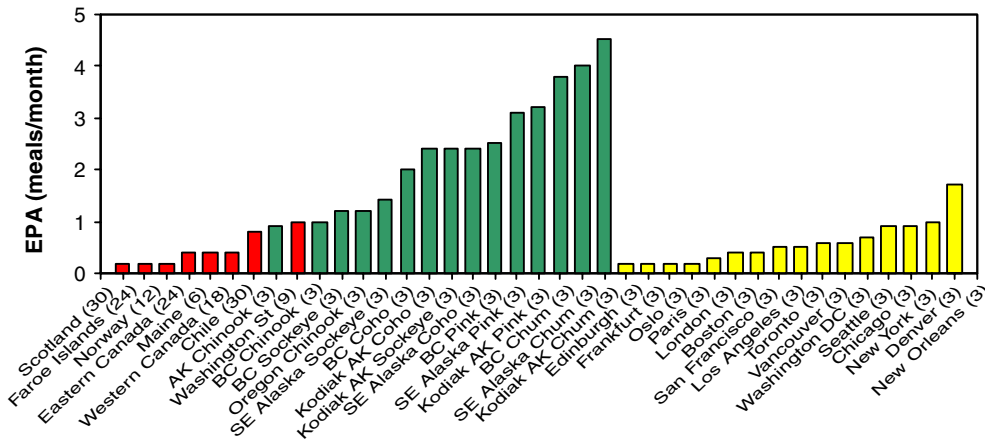


Fig. 5. Consumption advisories (in meals per month) based on USEPA cumulative carcinogenic risk assessment methods for total DDT, dieldrin, total chlordane, heptachlor epoxide, lindane, hexachlorobenzene, toxaphene, PCBs, and dioxins/furans for farmed salmon (red), wild salmon (green), and retail market salmon (yellow). The country in which the salmon was produced or the city from which it was purchased is indicated. The numbers in parentheses are the numbers of samples analyzed.

where the alterations in function are a result of developmental exposure and become life-long decrements.

The RfD for noncancer effects is set by USEPA on the basis of what is known to be the most sensitive endpoint. The noncancer RfD for PCBs, for example, was developed based on ocular and immunologic effects in monkeys (IRIS, 1999), but with acknowledgment that PCBs have been found to affect the hepatic, gastrointestinal, hematological, dermal, endocrine, neurological, and reproductive systems, and body weight as well. However, ATSDR (2000) indicates that neurobehavioral decrements may

occur at lower concentrations than other effects, including immunosuppression. For endrin, fewer organ systems are known to be affected but, while the RfD is set on the basis of neurological effects, endrin also causes birth defects and reproductive abnormalities. There is considerable uncertainty in much of this information, and thus the information available for noncancer risk assessment is incomplete. The uncertainty factors which are applied in the RfD development may or may not totally address the insufficiency of information. Furthermore, the USEPA advisory methods for noncancer effects specifically do not apply

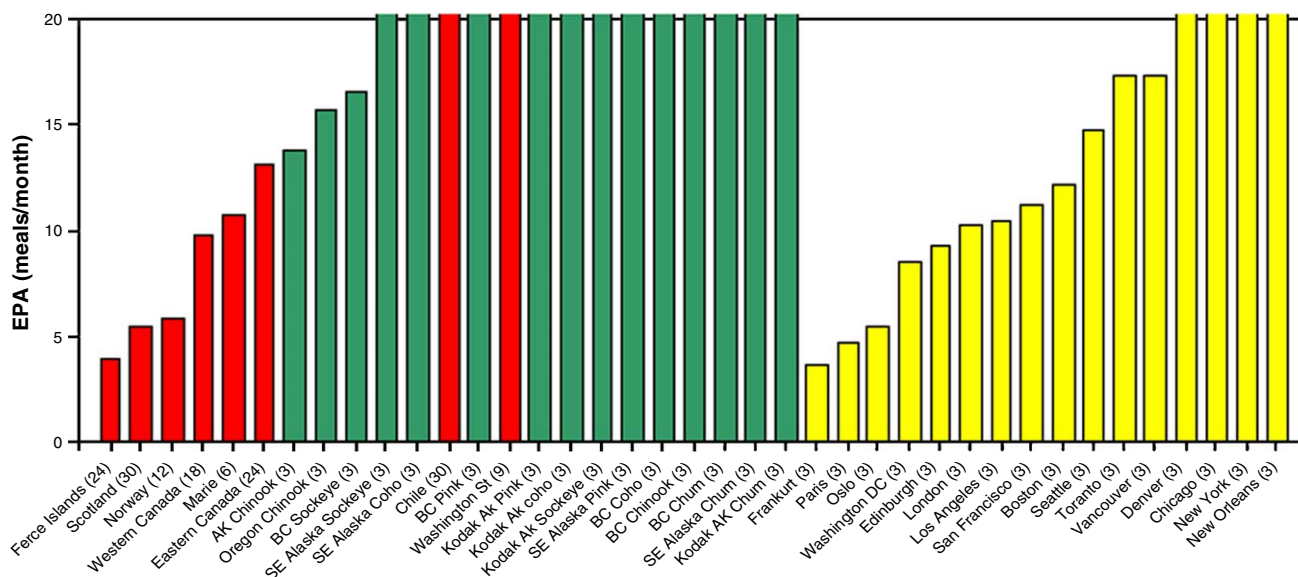


Fig. 6. Consumption advisories (in meals per month) for noncancer health effects based on USEPA RfD for endrin for (A) farmed (red) and wild (green) salmon and for (B) retail market salmon (yellow). The country in which the salmon was produced or the city from which it was purchased is indicated, and the number of samples analyzed is shown in parentheses.

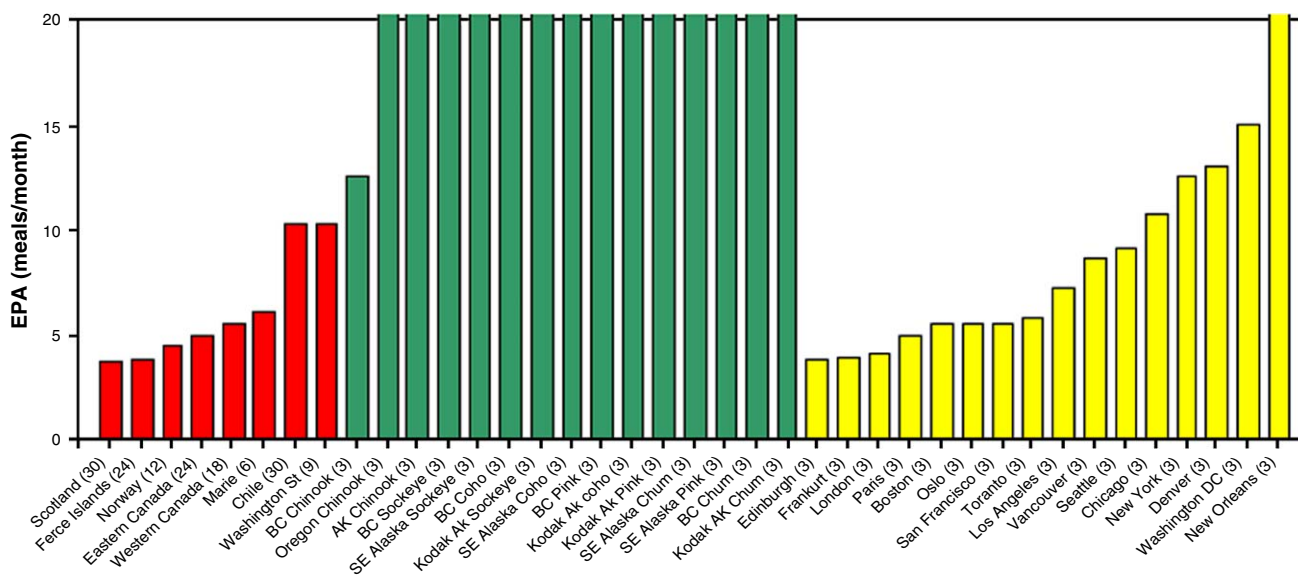


Fig. 7. Consumption advisories (in meals per month) for noncancer health effects for PCBs for farmed (red) and wild (green) salmon (A) and for retail market salmon (yellow) (B). The country in which the salmon was produced or the city from which it was purchased is indicated.

when contaminants have different mechanisms of action. This may be more the rule than the exception. For example, most pesticides and many of the PCB congeners do not bind to the Ah receptor, whereas dioxins and other PCB congeners do.

The noncancer health effects are very complex. For example, chlordane and its metabolites cause cell death, increase production of reactive oxygen species which accelerates lipid peroxidation and disrupts membranes, alter neurotransmitter levels in the brain, cause a reduction of bone marrow stem cells, and suppress gap junction communication (ATSDR, 1994).

When a person is exposed to two or more contaminants, the effects may be additive, less than additive, or more than additive. The default assumption is usually that the effects are additive (ATSDR, 2002). More than additive, or synergistic, actions are of particular concern, and there is some evidence that these do occur. For example, synergistic effects have been reported for chlordane and endrin, for toxaphene and chlordane (MIXTOX, 1992), for HCB and dioxin (ATSDR, 1996), and for *p,p'*-DDE and PCBs (ATSDR, 2002). With few exceptions, the mechanisms whereby synergistic effects occur are not well understood, but when they do occur, they are of significant public

health importance. The possibility of synergistic actions has not been considered in the advisory methods employed in this study.

Our results show that even wild Pacific salmon contain substantial levels of these contaminants and evoke consumption advisories based on USEPA methods. Chinook salmon, one of the largest and long-lived species and one most popular for fillets, contain enough of these carcinogens to trigger advisories in most samples of not more than one meal per month. Most of the other salmon commonly used in fillets, coho and sockeye, trigger advisories of about two meals per month. The chum and pink salmon, more frequently used for canned products, trigger less stringent advisories. These observations, in light of our previous demonstration that the source of the high levels in farmed salmon is the concentrated fish meal/fish oil obtained from ocean pelagic fish, indicate that we have sufficiently contaminated the oceans so that products from the ocean may pose human health hazards. Wild salmon, depending upon the species, feed on both zooplankton and fish. The food fed to the farmed salmon is mainly fish meal and fish oil, and is about 33% fat by weight. In contrast, the percentage fat in wild salmon is of the order of 6%, while farmed salmon, which get little exercise, have a lipid content of about 16% (Hamilton et al., 2005). Wild salmon, in addition to having to search for their food, eat lower on the food chain and, therefore, take in fewer contaminants.

It has been argued that most people eat more beef, pork, and chicken than salmon and that fat-soluble organochlorine compounds are present in these and all animal food fats. Therefore, because of the amount consumed, much of the human exposure to persistent organic compounds, perhaps even the majority of exposure, comes from foods other than salmon. This is probably true. While dioxin-like activity is found in almost all animal food products that contain fat, the levels in the farmed and market salmon that we have analyzed are higher than those in almost all other foods. The recent Institute of Medicine (IOM, 2003) report on dioxins and dioxin-like compounds in the food supply provides information on the amounts of dioxin-like compounds in foods studied in the Food and Drug Administration's total diet survey. Of some 250 food samples that were analyzed, the one sample of salmon (not identified as being either wild or farmed) had a larger TEQ than all but one other food sample. A major source of the contamination of other meats and animal products is the fish meal/fish oil and waste animal fats that are added as food supplements for cattle, pigs, and chickens (IOM, 2003). Persistent organochlorine compounds should clearly not be present in any food source. However, the fact remains that salmon, especially farmed salmon, contain higher levels of these contaminants than almost any other food.

These observations provide the solution to the problem. The solution is to stop the recycling of fish and animal fats into the feed of fish and animals that are to be used for

human consumption. The salmon aquaculture industry is reportedly making some progress in replacing fish meal/fish oils with vegetable-based food that contains much lower contaminant levels, and this process should be continued and expanded. Getting the contaminants out of other animal products requires similar action by other producers. IOM (2003) reports a study by PROMAR International (1999) which documents that every year some 8 billion pounds of waste animal fats are produced in slaughterhouses, and most are used as supplements in livestock feed. Since the onset of mad cow disease, we no longer feed beef fat to beef, but we continue to feed it to chickens and pigs, and feed the chicken and pig fat to beef. This process simply recycles fat-soluble contaminants back into the food supply, a practice that must be stopped.

While most organochlorine pesticides have not been manufactured in developed countries for a number of years, the fact that they are very persistent and that they have serious adverse health effects means that they remain a public health problem of significant magnitude. The fact that even wild Pacific salmon trigger cancer-based advisories indicates the extent to which we have polluted even the oceans. Our observations on levels of these compounds in both farmed and wild salmon indicate the need to both alter aquaculture methods and provide information to consumers that will allow them to make wise choices about the foods they eat.

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