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Geographic Differences in Persistent Organic Pollutant Levels of Yellowfin Tuna

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Background: Fish are a source of persistent organic pollutants (POPs) in the human diet. Although species, trophic level, and means of production are typically considered in predicting fish pollutant load, and thus recommendations of consumption, capture location is usually not accounted for.

Objectives: Yellowfin tuna (*Thunnus albacares*) are harvested from across the world's oceans and are widely consumed. Here, we determined geographic variation in the overall mass, concentration, and composition of POPs in yellowfin and examined the differences in levels of several POP congeners of potential relevance to human health.

Methods: We sampled dorsal muscle of 117 yellowfin tuna from 12 locations worldwide, and measured POP levels using combined liquid or gas chromatography and mass spectrometry according to U.S. Environmental Protection Agency standard procedures.

Results: POP levels varied significantly among sites, more than 36-fold on a mass basis. Individual fish levels ranged from 0.16 to 138.29 ng/g wet weight and lipid-normalized concentrations from 0.1 to 12.7 μM. Levels of 10 congeners that interfere with the cellular defense protein P-glycoprotein, termed transporter interfering compounds (TICs), ranged from 0.05 to 35.03 ng/g wet weight and from 0.03 to 3.32 μM in tuna lipid. Levels of TICs, and their individual congeners, were strongly associated with the overall POP load. Risk-based analysis of several carcinogenic POPs indicated that the fish with the highest levels of these potentially harmful compounds were clustered at specific geographic locations.

Conclusions: Capture location is an important consideration when assessing the level and risk of human exposure to POPs through ingestion of wild fish. https://doi.org/10.1289/EHP518

Introduction

Persistent organic pollutants (POPs) are hazardous environmental chemicals that bioaccumulate in animals and are routinely detected in humans (CDC 2009, 2015). Although global efforts to reduce their production and usage have resulted in corresponding declines in their environmental levels, reservoirs of these pollutants remain in the world's oceans (Lohmann et al. 2006). Fish can accumulate high amounts of these compounds as compared with other foods (Schecter et al. 2006b, 2010a) and thus consumption of seafood is an important route of human exposure to POPs. A better understanding of the factors governing levels of POPs in fish is essential to predict and reduce exposure.

Since POPs accumulate in fat and are eliminated slowly, the species and trophic level of fish have been previously used as indicators of relative pollutant load (Connolly and Pedersen 1988; Kelly et al. 2007). However, POP levels can also vary dramatically even within a single species or at a given trophic level, limiting the utility of these predictions. For instance, recent food basket surveys have shown that canned sardines, a relatively low trophic level species (Froese and Pauly 2000), can have higher levels of hexabromocyclododecanes (HBCDDs), organochlorine pesticides (OCPs), polybrominated diphenyl ethers (PBDEs), polychlorinated biphenyls (PCBs), and perfluorinated compounds (PFCs) than cod or salmon (Schecter et al. 2010c, 2010b, 2010a). Similarly, whereas it has been shown that pollutant levels also vary by species of fish, with the highest levels detected in oily fish (Knutsen et al. 2008; Smith and Gangolli 2002), differences in POP levels can also be detected within the same species based on means of production. For example, the levels of many POPs were higher in farmed versus wild salmon (Hites et al. 2004a).

A factor that may govern fish pollutant level is the patchy distribution of pollutants in the world's oceans. For less migratory fish species that remain in single regions for most of their life, this would be reflected in pollutant variation depending on location of capture. For example, high variation in the levels of OCPs, PBDEs, and PCBs were observed in wild skipjack (Ueno et al. 2003, 2004, 2005) depending on where they were captured. However, given the limited geographic scale of these studies, it seems plausible that even greater variation in POP levels would be observed when examining fish harvested from across the world's oceans. This geographic variation is important to address, because it has broad implications for assessment of health risks associated with POP exposure through consumption of fish.

Tuna are one of the most widely harvested fish in the world and among the top two fish species consumed in the United States, along with salmon (Loke et al. 2012). Among the tunas, yellowfin (*Thunnus albacares*) are the second most harvested species after skipjack (ISSF 2017). More than 1,200,000 metric tons of yellowfin are caught annually, accounting for 27% of the global tuna catch (ISSF 2017). Yellowfin are relatively large predatory fish, and most are sold as fresh or frozen fillets. Yellowfin are distributed globally, but have shorter ranges than bluefin (Block et al. 2011), and thus might be expected to reflect geographic trends in POP level variation.

Here, we measured POP levels in wild-caught yellowfin tuna from across the world's oceans and determined their wet weight and lipid-normalized concentrations. From these data we calculated the levels of specific POP congeners that we recently demonstrated to be inhibitors of transporter proteins act as important cellular defense in humans (Nicklisch et al. 2016), termed TICs. The results of this study demonstrate the important role of geographic origin on total pollutant level of fish and reveal a close association between TICs and overall POP load.

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Table 1. Panel of persistent organic pollutants (POPs) screened in yellowfin tuna.

OCPs	PBDEs	PCBs					
Hexachlorobenzene	BDE–28 + 33	PCB-1	PCB-35	PCB-73	PCB-120	PCB-158	PCB-194
HCH, alpha	BDE-47	PCB-2	PCB-36	PCB-77	PCB-121	PCB-159	PCB-195
HCH, beta	BDE-99	PCB-3	PCB-37	PCB-78	PCB-122	PCB-161	PCB-196
HCH, gamma	BDE-100	PCB-4	PCB-38	PCB-79	PCB-123	PCB-162	PCB–197 + 200
Heptachlor	BDE-153	PCB-5	PCB-39	PCB-80	PCB-126	PCB-164	PCB–198 + 199
Aldrin	BDE-154	PCB-6	PCB–40 + 41 + 71	PCB-81	PCB-127	PCB-165	PCB-201
Chlordane, oxy-	BDE-183	PCB-7	PCB-42	PCB-82	PCB–128 + 166	PCB-167	PCB-202
Chlordane, gamma (*trans*)	BDE-209	PCB-8	PCB-43	PCB–83 + 99	PCB–129 + 138 + 160 + 163	PCB-169	PCB-203
Chlordane, alpha (*cis*)		PCB-9	PCB–44 + 47 + 65	PCB-84	PCB-130	PCB-170	PCB-204
Nonachlor, *trans*-		PCB-10	PCB–45 + 51	PCB–85 + 116 + 117	PCB-131	PCB–171 + 173	PCB-205
Nonachlor, *cis*-		PCB-11	PCB-46	PCB–86 + 87 + 97 + 108 + 119 + 125	PCB-132	PCB-172	PCB-206
2,4′-DDD		PCB–12 + 13	PCB-48	PCB–88 + 91	PCB-133	PCB-174	PCB-207
4,4′-DDD		PCB-14	PCB–49 + 69	PCB-89	PCB–134 + 143	PCB-175	PCB-208
2,4′-DDE		PCB-15	PCB–50 + 53	PCB–90 + 101 + 113	PCB–135 + 151 + 154	PCB-176	PCB-209
4,4′-DDE		PCB-16	PCB-52	PCB-92	PCB-136	PCB-177	
2,4′-DDT		PCB-17	PCB-54	PCB–93 + 95 + 98 + 100 + 102	PCB-137	PCB-178	
4,4′-DDT		PCB–18 + 30	PCB-55	PCB-94	PCB–139 + 140	PCB-179	
Mirex		PCB-19	PCB-56	PCB-96	PCB-141	PCB–180 + 193	
HCH, delta		PCB–20 + 28	PCB-57	PCB-103	PCB-142	PCB-181	
Heptachlor epoxide		PCB–21 + 33	PCB-58	PCB-104	PCB-144	PCB-182	
alpha-Endosulfan		PCB-22	PCB–59 + 62 + 75	PCB-105	PCB-145	PCB–183 + 185	
Dieldrin		PCB-23	PCB-60	PCB-106	PCB-146	PCB-184	
Endrin		PCB-24	PCB–61 + 70 + 74 + 76	PCB–107 + 124	PCB–147 + 149	PCB-186	
beta-Endosulfan		PCB-25	PCB-63	PCB-109	PCB-148	PCB-187	
Endosulfan sulfate		PCB–26 + 29	PCB-64	PCB–110 + 115	PCB-150	PCB-188	
Endrin aldehyde		PCB-27	PCB-66	PCB-111	PCB-152	PCB-189	
Endrin ketone		PCB-31	PCB-67	PCB-112	PCB–153 + 168	PCB-190	
Methoxychlor		PCB-32	PCB-68	PCB-114	PCB-155	PCB-191	
Technical toxaphene		PCB-34	PCB-72	PCB-118	PCB–156 + 157	PCB-192	

Note: Co-eluting congeners are preceded with a plus symbol. The previously identified (Nicklisch et al. 2016) transporter interfering compounds (TICs): 4,4′-DDD, 4,4′-DDE, 4,4′-DDT, Dieldrin, Endrin, BDE-47, BDE-100, PCB-146, PCB-170, PCB-187.

Methods

Tuna Collection

Dorsal, white muscle filets of yellowfin tuna (*Thunnus albacares*) were collected from all four major yellowfin stocks, including the Atlantic Ocean, Eastern Pacific Ocean, Western Pacific Ocean, and Indian Ocean stocks (ISSF 2017). The 12 capture locations (see Figure S1) included the North Pacific Ocean (NPO), North East Pacific Ocean (NEPO), Gulf of Mexico (GOM), South East Pacific Ocean (SEPO), Northwest Atlantic (NWAO), Northeast Atlantic Ocean (NEAO), South East Atlantic Ocean (SEAO), Indian Ocean (IO), South China Sea (SCS), North China Sea (NCS), Northwest Pacific Ocean (NWPO), and the Southwest Pacific Ocean (SWPO). The target size class for sampling was 100 cm, roughly 1–2 y old (Kikkawa and Cushing 2002), and the sampled fish had a mean standard length of 92.91 ± 21.98 cm, with a range of 52.32–139.5 cm. Only fork length measurement was available for fish from the IO. Tuna were captured either by trolling or longline. A coordinate for the capture site was recorded for each fish, accurate to within 100 km.

Pollutant Analysis

Tuna muscles were sent to AXYS (AXYS Analytical Services Ltd.) for analysis. POPs were measured according to the following U.S. Environmental Protection Agency (EPA) methods for OCPs: 608, 625, 1625, 8081, 8270; PBDEs: 1614, 625, and PCBs: 1668, 8270. Analysis of OCPs was performed on a DB-5 capillary chromatography column coupled to a high-resolution mass spectrometer (HRMS). The concentrations of all 209 PCB congeners were determined by high-resolution gas chromatography (HRGC) on an SPB-Octyl column coupled to a high-resolution mass spectrometer (HRMS). Analysis of the PBDE congeners was performed using HRGC on a DB-5HT capillary column coupled to an HRMS.

All 117 tuna from the 12 sites were screened for 29 OCPs, 11 of these sites (109 tuna) were also screened for 209 PCBs, and at eight of these sites (79 tuna) were analyzed for nine PBDEs (Tables 1 and 2; see also Figure S1). Total POP levels were defined as the sum of all OCPs, PBDEs, and PCBs measured in fish from the eight sites with full coverage. One fish from the GOM had 4.8-fold higher total POP levels than any other fish and was more than two times the interquartile range within the GOM sample group, and thus was excluded from further analysis.

In figures where individual POPs were assigned to different groups, we grouped PCBs according to their backbone chlorination into mono-, di-, tri-, tetra-, penta-, hexa-, hepta-, octa, and nonachlorinated biphenyls. The OCP congeners were grouped as follows: DDT (4,4′-DDT, 2,4′-DDT, 4,4′-DDE, 2,4′-DDE, 4,4′-DDD, 2,4′-DDD, methoxychlor); Chlordane (oxy-chlordane, γ-(*trans*)-chlordane, α-(cis)-chlordane, *trans*-nonachlor, *cis*-nonachlor); endosulfan (α-endosulfan, β-endosulfan, endosulfan sulfate, heptachlor, heptachlor epoxide); endrin (Aldrin, dieldrin, endrin, endrin aldehyde, endrin ketone); HCH (α-hexachlorocyclohexane, β-hexachlorocyclohexane, γ-hexachlorocyclohexane, δ-hexachlorocyclohexane). Hexachlorobenzene (HCB), mirex, and toxaphene were used as single compounds.

Statistics and Data Analysis

Blank correction and analyses of pollutant raw data were performed according to previous studies (Hites et al. 2004b;

Table 2. Metadata on wild yellowfin tuna analyzed in this study.

Site	Samples [n]	Standard Length [cm]	Lipids [%]	OCPs [ng/g ww]	PBDEs [ng/g ww]	PCBs [ng/g ww]	Total POPs [ng/g ww]	Total POPs [μM]	TICs [μM]	TIC fraction [%]
North Pacific Ocean (NPO)	10	117.35 ± 19.06	1.52 ± 1.16	3.40 ± 3.65	NA	3.40 ± 2.98	NA	NA	NA	NA
Northeast Pacific Ocean (NEPO)	10	55.87 ± 1.97	3.25 ± 1.12	7.86 ± 3.50	1.06 ± 1.20	3.38 ± 2.65	12.29 ± 6.86	1.05 ± 0.47	0.44 ± 0.22	42
Gulf of Mexico (GOM)	8	99.85 ± 8.16	0.93 ± 0.62	1.62 ± 1.17	0.35 ± 0.21	8.08 ± 5.08	10.05 ± 6.26	4.34 ± 4.57	1.01 ± 1.07	23
Southeast Pacific Ocean (SEPO)	10	71.45 ± 3.99	1.23 ± 0.85	0.49 ± 0.47	NA	0.55 ± 0.33	NA	NA	NA	NA
Northwest Atlantic Ocean (NWAO)	10	92.80 ± 3.49	0.41 ± 0.16	1.06 ± 0.28	0.21 ± 0.11	3.82 ± 1.28	5.09 ± 1.42	4.18 ± 2.94	1.12 ± 0.76	27
Northeast Atlantic Ocean (NEAO)	10	80.42 ± 7.13	6.08 ± 2.56	8.23 ± 3.35	0.18 ± 0.06	6.52 ± 2.47	14.93 ± 5.44	0.68 ± 0.20	0.16 ± 0.04	24
Southeast Atlantic Ocean (SEAO)	8	84.94 ± 23.22	2.76 ± 1.38	3.22 ± 1.35	NA	NA	NA	NA	NA	NA
Indian Ocean (IO)	10	97.07 ± 2.32[a]	0.60 ± 0.18	0.43 ± 0.18	0.03 ± 0.07	0.23 ± 0.10	0.69 ± 0.30	0.35 ± 0.16	0.19 ± 0.09	54
South China Sea (SCS)	10	109.4 ± 8.60	1.09 ± 0.58	0.93 ± 0.58	0.10 ± 0.07	0.69 ± 0.41	1.72 ± 1.05	0.49 ± 0.33	0.24 ± 0.18	50
North China Sea (NCS)	10	96.9 ± 3.67	0.71 ± 0.60	1.42 ± 1.38	NA	1.25 ± 0.90	NA	NA	NA	NA
Northwest Pacific Ocean (NWPO)	10	100.45 ± 1.15	0.68 ± 0.20	0.20 ± 0.11	0.09 ± 0.12	0.12 ± 0.04	0.41 ± 0.16	0.14 ± 0.04	0.04 ± 0.02	30
Southwest Pacific Ocean (SWPO)	10	108.25 ± 25.93	0.62 ± 0.45	0.27 ± 0.12	0.05 ± 0.03	0.22 ± 0.10	0.54 ± 0.21	0.27 ± 0.14	0.09 ± 0.04	32

Note: Listed are the means ± SD of standard length and weight % of total lipids in tuna. The sum of the means ± SD of OCPs, PBDEs, PCBs, and total POPs for each site is shown in ng/g wet weight. In addition, the sum of the means ± SD of total POPs and the 10 transporter-inhibiting compounds (TICs) are listed as micromolar (μM) concentration in the lipid phase. The micromolar fraction of the 10 inhibitors relative to total POPs is listed in percent. Where compounds were not measured values are indicated as not available (NA).
[a]Fork length.

Schecter et al. 2006b). Briefly, where sample values were below the detection limit the values were treated as nondetectable. Most blank measurements were at or below the detection limits and thus not subtracted from samples. In runs where blank values were above detection limits, only samples with values more than twice the blank value were reported (after subtraction of the blank value). The remaining values were treated as nondetectable. The nondetectable values were assigned zero when calculating the molar concentrations of POPs in the lipid fraction of the muscle tissue, and for further statistical analysis, so as not to overestimate the level of pollutant in samples.

To relate the measured POP levels in tuna to effective concentrations of transporter inhibiting compounds (TICs) from our previous study (Nicklisch et al. 2016), we calculated the lipid-normalized levels of total POPs and the 10 TICs across sites (Table 2), assuming a lipid mass density of 1 (Young 1986). Sample tissue lipid content was determined gravimetrically (AXYS Analytical Services Ltd.) and expressed as percent of sample weight. For each normalization, we used the respective congener molecular weight derived from the National Institutes of Health (NIH) Pubchem database (https://pubchem.ncbi.nlm.nih.gov/).

To meet assumptions of normality and homogeneity of variance, all data were $\log_{10}$-transformed. For this, sample distributions were initially analyzed using JMP's normal quantile plots and then $\log_{10}$–transformed to approximate the normal distribution. Analysis of variance (ANOVA) was then performed to test the null hypotheses of equal means between groups. A post hoc Tukey honest significant difference (HSD) test was conducted to identify significant pairwise differences between these groups. We also validated the significance of differences between medians using a Kruskal-Wallis rank sum test on the nontransformed data. Data were analyzed and plotted using JMP Pro version 12 (http://www.jmp.com) and OriginPro 2016 (http://www.originlab.com).

A principal components analysis was conducted to explore covariance among TICs (Nicklisch et al. 2016) and the total POP levels in 78 fish for which all 247 POPs were measured (see Figure S1). We performed the PCA on a covariance matrix because all our variables had the same units of measure, and their log-transformed data were normally distributed, with similar scales and ranges. Nondetects were treated as zero values. To address any potential effect of nondetects (i.e., missing values), we used the restricted maximum likelihood (REML) estimation method for calculating covariance according to JMP Pro version 12. The TIC endrin was detected in only three fish from the NEAO and was thus excluded from PCA analysis.

Risk-Based Consumption Advisory Calculations

We used the U.S. EPA's modified approach for multiple contaminants in a single fish species to calculate consumption limits based on the carcinogenic effects of several POPs, including total PCBs, dieldrin, and toxaphene (Hites et al. 2004a; U.S. EPA 2000). Consumption limits were calculated for 108 tuna from the 11 sites (see Figure S1) where all three of these pollutant classes were measured. Current cancer slope factors (CSFs) were derived from the U.S. EPA's Integrated Risk Information System (IRIS) database, searched through the NIH Toxnet data network (https://toxnet.nlm.nih.gov/). For PCBs, the more conservative upper-bound slope factor of 2 (mg/kg body weight)/d was chosen. Oral slope factors for dieldrin and toxaphene were 16 and 1.1 (mg/kg body weight)/d. For all monthly consumption limit calculations, we used the measured contaminant concentrations in tuna muscle in mg/kg, an acceptable risk level (ARL) of 10^{-5}, an adult consumer body weight of 70 kg, and an average uncooked fish meal size of 227 g (8 oz).

For the nutritional recommendation thresholds, we used the Food and Drug Administration (FDA) and the U.S. EPA joint fish consumption advice (FDA 2014) to consume 340 g (12 oz) of cooked fish a week (DHHS, USDA 2015) the diet recommendation from the American Heart Association (AHA) to eat fish at least two times per week with a single serving size of 99 g (3.5 oz) of cooked fish (AHA 2015; Kris-Etherton et al. 2002). We used a conversion factor of 1.33 to convert the mass of cooked fish

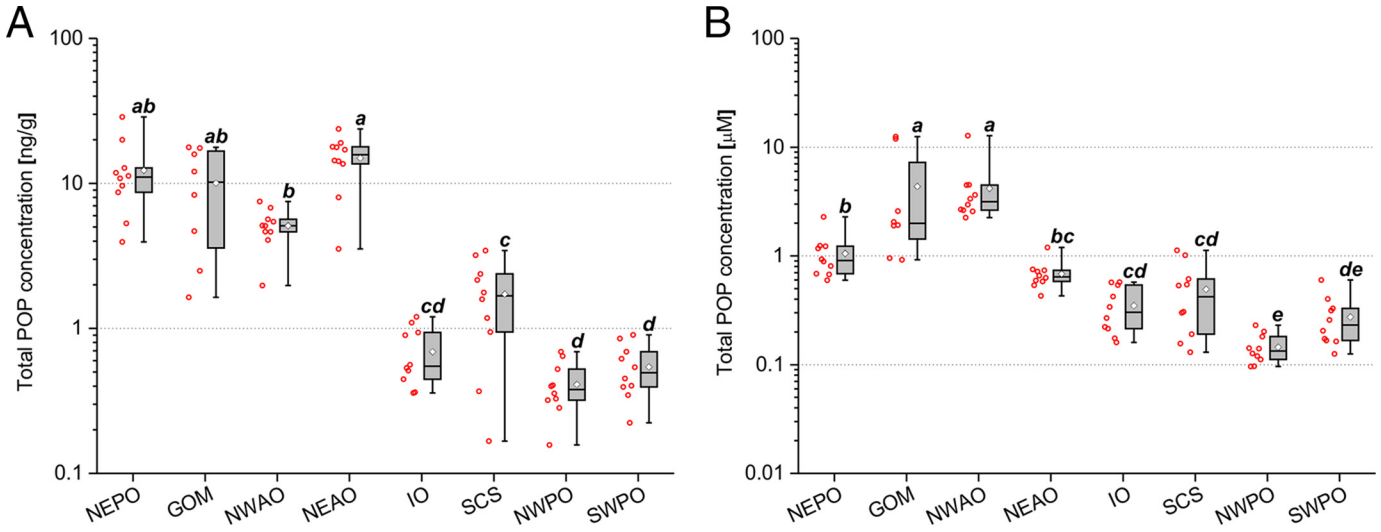

Figure 1. Variation of POP levels in wild yellowfin tuna (*Thunnus albacares*) captured at different locations across the globe. (*A*) Levels of total POPs across eight capture locations on a mass basis. (*B*) Lipid-normalized total POP concentrations across the eight sites. Whiskers represent the minimum and maximum values. Diamonds represent the mean values. The horizontal line represents the 50th percentile, and the box represents the 25th and 75th percentiles. The red hollow spheres to the left of each box plot display the individual fish values. Letters in parenthesis represent subgroups of the sample population with means that were significantly different from each other upon $\log_{10}$-transformation and using Tukey's post hoc analysis. Note: GOM, Gulf of Mexico; IO, Indian Ocean; NEAO, Northeast Atlantic Ocean; NEPO, Northeast Pacific Ocean; NWAO, Northwest Atlantic Ocean; NWPO, Northwest Pacific Ocean; SWPO, Southwest Pacific Ocean.

to a corresponding mass of uncooked fish (Minnesota Department of Health 2016). Monthly dietary intake recommendations were calculated based on an average of 4.33 weeks per month.

Results

Tuna Pollutant Levels Depend on Geographic Origin of Fish

We observed large variation in pollutant levels among the tuna. On a mass basis, mean total pollutant levels varied by a factor of 36 between sites (Figure 1A) and were significantly different across sites [$F = 55.56$, $p = < 0.0001$, with degrees of freedom $(df) = (7,70)$]. In general, tuna caught from the four sites in the offshore waters of North America and Europe had total POP concentrations that were on average more than an order of magnitude higher than in fish from the four sites located in the waters of Asia and Oceania (Figure 1A; see also Figure S1). Yellowfin from the NWPO and SWPO tended to be the least contaminated fish, whereas the highest levels of POPs were observed in the NEPO, GOM, and NEAO. Given that POPs are hydrophobic and predominantly accumulate in fat, we also calculated the lipid-adjusted concentrations of total POPs for the tuna from all eight capture locations (Figure 1B). As with pollutant mass, there were significant geographic differences in total POP concentrations across all sites [$F = 40.66$, $p = < 0.0001$, with $df = (7,70)$].

Among individual fish, the mass-based levels in the most and least contaminated tuna varied by a factor of 180 (see Figure S2A). The 10 most polluted fish were caught in the NEAO, NEPO, and GOM, with total POP levels of the top 3 fish ranging from 20 to about 29 ng/g wet weight. In contrast, the 10 least contaminated fish were all from the IO, SCS, NWPO, and SWPO and had total POP levels ranging from 0.2 to 0.4 ng/g wet weight, > 2 orders of magnitude lower than the highest fish (see Figure S2A). Similarly, the lipid-normalized total POP concentrations in individual tuna varied more than 130-fold, ranging from 0.1 μM in the NWPO to 12.72 μM in the NWAO (see Figure S2B).

Fish with higher fat percentages generally had higher amounts of POPs on a mass basis (Figure 2A). This was most evident when comparing fish caught in the NEPO and NEAO, which showed higher total pollutant levels with an increase in the lipid content (Figure 2A). However, the correlation of pollutant mass with lipid content was modest ($R^2 = 0.54$) and was not always indicative of total POP load. For instance, fish caught in the GOM had average lipid levels of 0.93% and total POP concentrations of 10.05 ng/g wet weight, which were significantly higher ($p < 0.0001$) than fish from the SCS with similar lipid concentrations of 1.09% with total POP levels of only 1.72 ng/g wet weight (Table 2).

POP levels were also largely independent of the size of fish ($R^2 = 0.22$; Figure 2B). Individuals from the NEPO, NEAO, and GOM showed the greatest variations in total pollutant levels while having the lowest variations in standard lengths (Figure 2B). For instance, fish caught from the NEPO had the shortest mean standard lengths of 56 cm, but total POP levels of 12.3 ng/g wet weight. In contrast, fish caught in the SWPO were almost double this size, with a mean standard length of 108 cm, yet had total levels of 0.5 ng/g, wet weight (Table 2).

An important observation was that when the POP levels were lipid normalized, the resulting concentrations across fish showed even greater independence from both lipid content ($R^2 = 0.01$; Figure 2C) and length ($R^2 = 0.01$; Figure 2D). Indeed, fish caught from the GOM and NWAO had the highest POP concentrations, despite having the lowest lipid content. For example, two fish from the GOM and one fish from the NWAO had total POP concentrations of 11.9, 12.5, and 12.7 μM while having lipid levels of 0.36%, 0.39%, and 0.16% (Figure 2C; see also Figure S2B).

Differences in the Contribution of POP Classes to Total POP Levels

Next we examined the contributions of OCPs, PBDEs, and PCBs to the observed differences in total POP levels across the eight sites for which all three pollutant classes were measured (Table 2; see also Figure S1). With the exception of the NWAO and

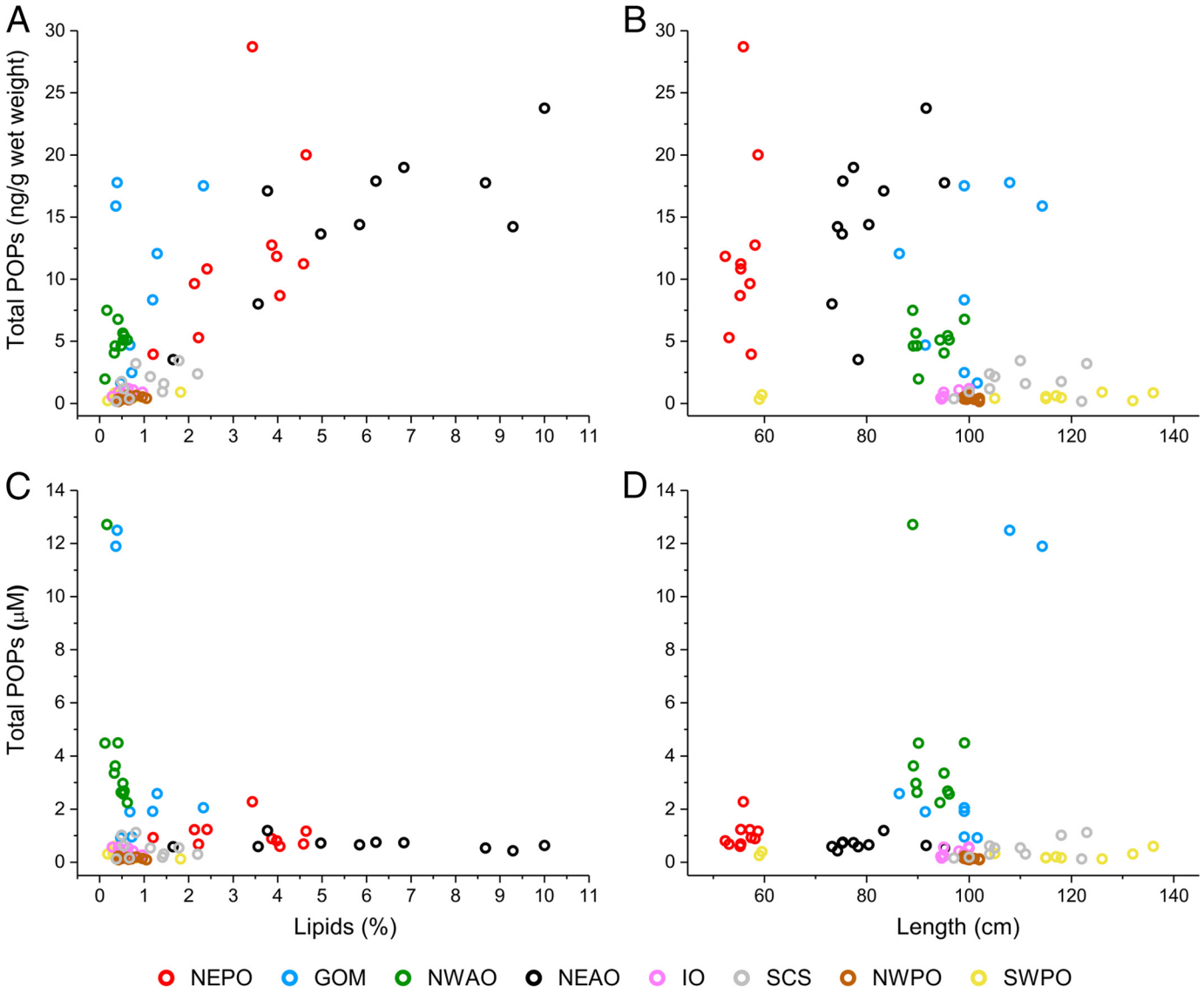

Figure 2. Relationships between fish length or lipid content and the levels or concentrations of POPs. (*A*) POP levels, on a mass basis, of each fish versus lipid content. (*B*) POP levels, on a mass basis, of each individual fish against length. (*C*) POP concentrations of each individual fish against lipid content. (*D*) POP concentrations of each individual fish against length.

GOM, the relative ratios of the three POP classes were similar across sites (Figure 3A). PBDEs typically accounted for only a small fraction of the total pollutant load (1–9%). In the SWPO, NWPO, SCS, IO, NEAO, and NEPO, about 49–64% of the total POP levels were attributed to OCPs, whereas PCBs contributed 28–44% (Figure 3A). However, in two of the four more polluted sites, about 75% (NWAO) and 80% (GOM) of the total POPs were PCBs. When comparing pollutant levels across sites, the geographic variation pattern observed for total POP levels was mostly conserved for PCBs and PBDEs, whereas OCP levels varied independently of the overall POP load (Figure 1A and Figure 3B–D).

Specific Pollutant Congeners Account for a Large Fraction of the OCPs and PBDEs at Certain Sites

For both OCPs and PBDEs, the congeners comprising each group varied by location (Figure 4A,B; see also Figure S3C). For example, among OCPs, the major contributor to the total levels were typically the DDTs, representing 48–88% of the total OCP levels across nine sites (Figure 4A; see also Figure S3C). However, in the NEAO and the SWPO, toxaphene (56%) and mirex (53%) had the highest relative fractions of total OCPs (Figure 4A). Similarly, among PBDEs, the single congeners BDE-47 (44–65%) and BDE-100 (14–26%) were the major contributors among the most contaminated sites in the NEPO, GOM, NWAO, and NEAO (Figure 4B). However, in the least contaminated sites, the NWPO fish had 86% of the total PBDEs contributed by BDE-209, whereas in the IO the major contributor was BDE-99 (34%).

The exception to this variation in congener levels by location was seen in the PCBs, which when grouped according to their backbone chlorination showed no apparent site-specific difference in relative ratios. For instance, the combined group of hexa-chlorinated biphenyls ($n = 31$) had the highest relative contribution to the total PCB levels, ranging from 40% to 51% across all 11 sites (Figure 4C; see also Figures S1 and S3D). These constant ratios of grouped PCB congeners were independent of the total PCB levels (Figures 3D and 4C; see also Figure S3B,D), perhaps reflecting global dispersion of PCBs and/or similar abiotic or biotic metabolism of these congeners.

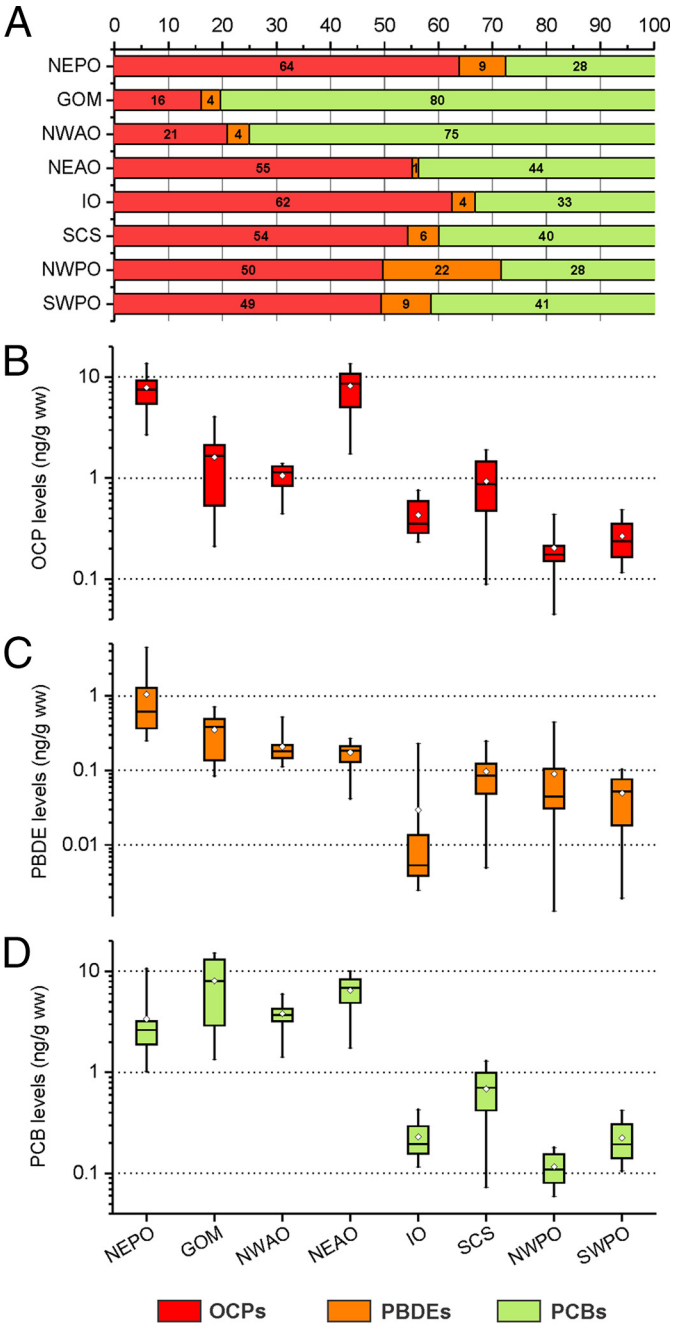

Figure 3. Geographic distributions and relative contributions of pollutant classes (OCPs, PBDEs, and PCBs) to total POP levels. Percentage contribution of OCPs, PBDEs, and PCBs to the total POP level (*A*) and ranges of concentrations of the 29 OCPs (*B*), 9 PBDEs (*C*), and 209 PCBs (*D*) in ng/g wet weight for tuna from eight sampling sites. Whiskers represent minimum and maximum values for each site. Diamonds represent the mean values. The horizontal line represents the 50th percentile, and the box represents the 25th and 75th percentiles.

Levels of TICs

Although persistent pollutants are typically present in fish at low levels, it is well known that chronic low-level POP exposure can have unanticipated effects, such as endocrine disruption or reproductive toxicity. One of these effects could be an adverse impact on the cell protection mechanisms operating in humans (and other animals). P-glycoprotein (P-gp) is a protective drug transporter that can bind a wide range of small hydrophobic molecules (Aller et al. 2009; Gottesman et al. 2002). It is typically expressed at the environmental barrier sites of animals, such as the intestine and gills, where it acts to keep harmful substances out of the body (Döring and Petzinger 2014; Sturm and Segner 2005). Interestingly, although P-gp binds some POPs (Nicklisch et al. 2016), it appears to be relatively ineffective at eliminating them, as evidenced by their ready bioaccumulation. These TICs could reduce the effectiveness of P-gp (Nicklisch et al. 2016).

To determine environmental levels of TICs, we examined how their concentrations differed among sites (Figure 5A and Table 2). Similar to the lipid-normalized total POP concentrations, TIC concentrations were significantly different among sites [$F = 31.75$, $p = < 0.0001$, with $df = (7,70)$], with the lowest mean levels of 0.04 μM detected in the NWPO and the highest mean concentrations of 1.12 μM in the NWAO (Figure 5B). The average TIC concentrations varied as much as 28-fold across all sites (Figure 5B and Table 2). Among individual fish, the top 10 most polluted fish were from the NWAO, GOM, and NEPO, whereas the 10 least contaminated fish came from the NWPO, SWPO, and SCS (see Figure S2C). The three most contaminated fish had TIC levels ranging from 2.83 to about 3.32 μM. On a mass basis, the geographic variation of TIC levels was also significant [$F = 33.58$, $p = < 0.0001$, with $df = (7,70)$] and highly similar to the total POPs (Figures 1A and 5C). Mass-based TIC levels from the most contaminated to the least contaminated fish varied almost 240-fold, ranging from 0.05 to about 12.52 ng/g wet weight (see Figure S2D).

A principal components analysis of the concentrations of individual TICs and the remaining total POP concentrations (Total-TICs) revealed that 83.3% (lipid normalized) and 85.3% (mass based) of the variability was described along the first principal component (PC1) axis (Figure 6A,B). Most notable was the pattern of positive correlation across both regions and individual fish, reflecting high co-variation of the identified TICs with each other, and with the sum of the remaining POPs. Regions were largely distributed along a POP concentration gradient, with lower total POP levels (NWPO, SWPO, SCS, IO) negatively associated with PC1, whereas regions with higher POP levels (NEPO, GOM, NWAO) were positively associated with PC1.

Impact of Geographic Variation on Risk-Based Consumption Levels

To better understand the impact of geographic variation in POP levels on potential health risks through fish consumption from different sites, we took the approach of Hites et al. (2004a), which explored the cancer risk of PCBs, toxaphene, and dieldrin in farmed versus wild salmon. The results indicated that the large variation in total POP levels would also be reflected in significant differences [$F = 37.39$, $p = < 0.0001$, with $df = (10, 97)$] in potential meal recommendations of tuna among sites (Figure 7). Importantly, the most restrictive consumption advisories were clustered at certain sites. For instance, for 9 of 10 fish in the NEAO the calculated meal consumption advice was below the AHA or FDA recommended monthly advice on nutritional fish intake (Figure 7). Similarly, five of eight fish from the GOM had contaminant levels that might trigger advice for fish consumption limits below the minimum recommended dietary intake.

Calculated meal recommendations based on the levels measured in individual fish varied from as many as 787 meals/mo in one fish from the NWPO down to only 3 meals/mo in fish from the NEAO, GOM, NEPO, and NPO (Figure 7). Although recommended meals per month were unrestricted (i.e., >16 meals/mo) (U.S. EPA 2000) for 67% of the tuna, 20% of the fish had recommended meal levels below FDA's nutritional value advice for pregnant

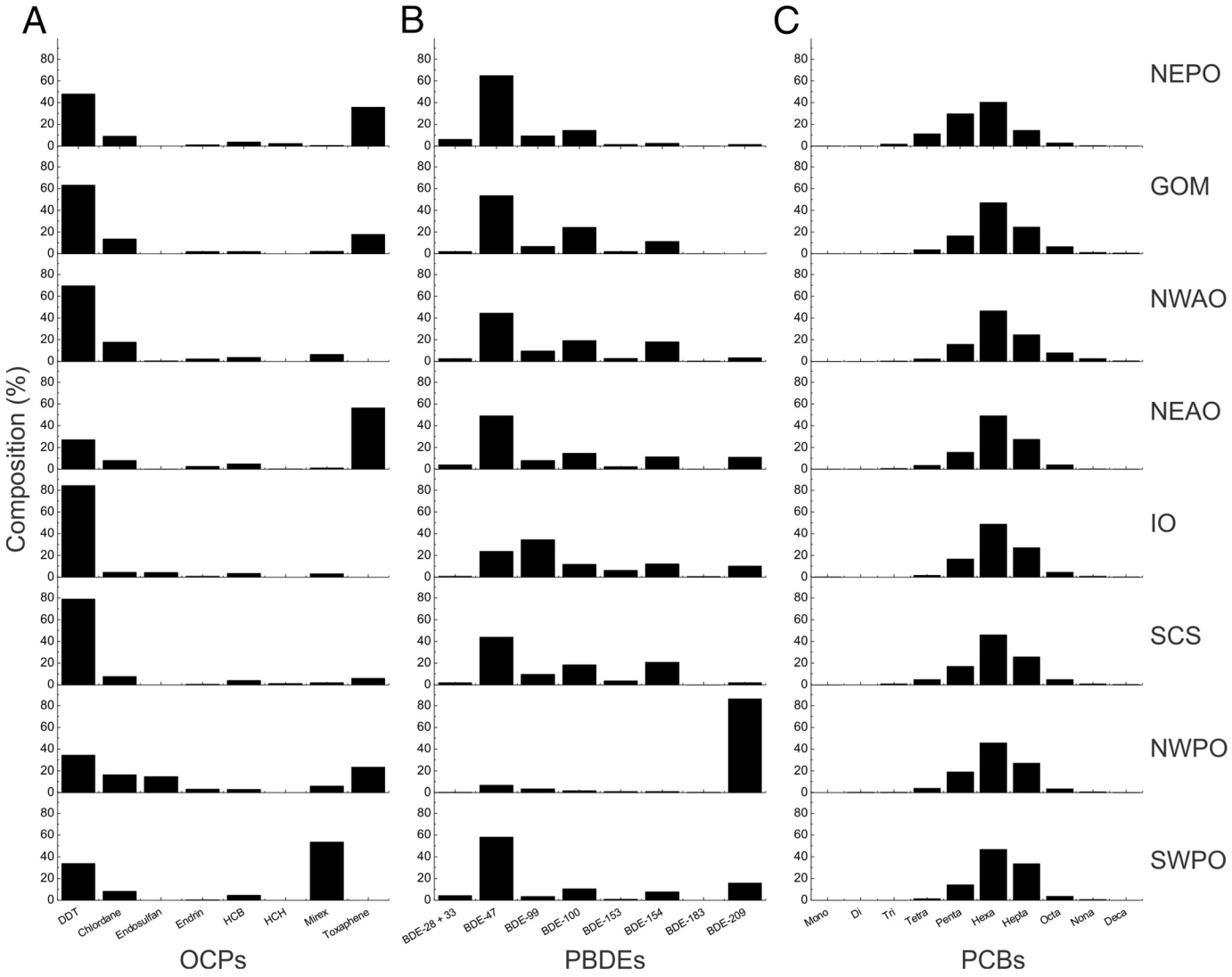

Figure 4. Relative contributions of individual congeners to the total of each pollutant class. The percentage of each congener group relative to the total levels of OCPs (*A*), PBDEs (*B*), or PCBs (*C*). The POP compounds were grouped according to their occurrence in technical mixtures or common chemical structures. Due to co-elution of BDE-28 and BDE-33, the sum of both congeners is shown. The PCB congeners were grouped according to their amount of backbone chlorination. Note: DDT, dichloro-diphenyl-trichloroethane; HCB, hexachlorobenzene; HCH, hexachlorocyclohexane.

and breastfeeding women of >9 meals/mo (FDA 2014; DHHS, USDA 2015). Importantly, 13% of the fish had levels of POPs that resulted in meal levels at or below the AHA's recommended level of >5 meals/mo.

Discussion

This study demonstrates that pollutants in tuna can vary dramatically by location of capture, with implications for managing the risk of human exposure to harmful chemicals in fish. These dramatic differences likely ensue from a multitude of factors including historical deposition, atmospheric transport effects and/or local circulation patterns (Atlas and Giam 1981; Beyer et al. 2000; Jepson and Law 2016; Parnell et al. 2008; Santschi et al. 2001; Welsh and Inoue 2000). Our results indicated that simple indirect measures such as species, size, or lipid content may not necessarily be adequate to predict the differences in total levels of pollutants among fish. On a mass basis total POP levels were only modestly ($R^2 = 0.54$) correlated with lipid content and poorly correlated with size ($R^2 = 0.22$). The correlation between lipid levels and POP content was even less robust when levels were calculated on a concentration basis. For instance, three fish with the highest POP concentrations had among lowest lipid levels (Figure 2C). However, we noticed that these fish also had high levels of PCBs, which could indicate that PCBs have a higher equilibrium concentration in tuna fat as compared to OCPs or PBDEs, and/or that a combination of exposure period, bioavailability, and pollutant distribution patterns act to enhance PCB uptake (Morgan and Lohmann 2010; van der Oost et al. 1996; Verweij et al. 2004).

Potential Sources of POPs in Yellowfin Tuna

Organochlorine pesticides. The DDT group was largely the most prominent contributor of total OCPs across all tested sites. In the NEPO and the NEAO about 64% and 55% of the total POP levels of 12.3 and 14.9 ng/g wet weight were attributed to OCPs, leading to a highly similar OCP load in these fish of 7.9 and 8.2 ng/g wet weight (Table 2). Close to the site of catch in the NEPO, an estimated 870–1,450 tons of DTT were discharged into the Palos

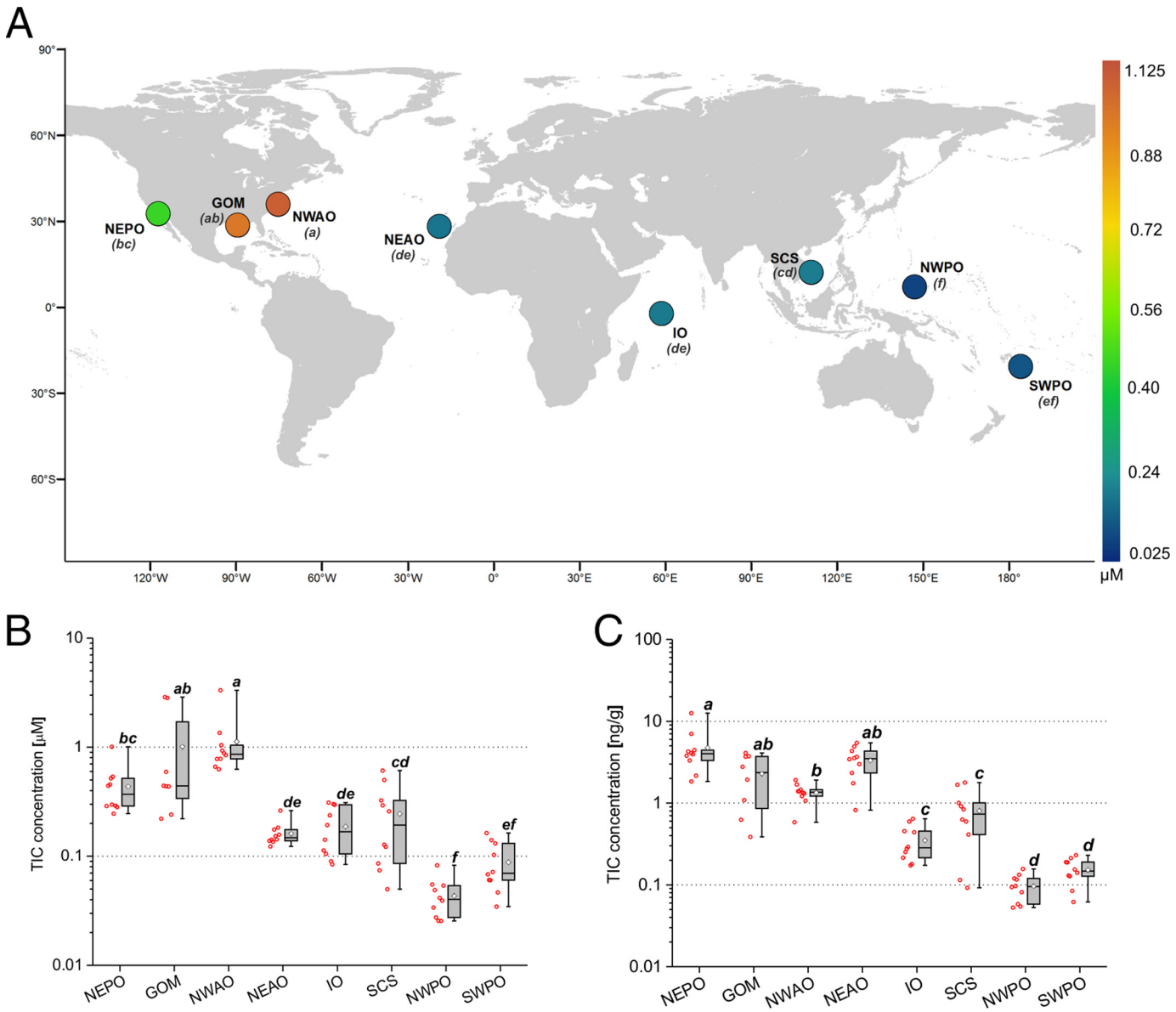

Figure 5. Levels of transporter interfering compounds (TICs) in yellowfin tuna. (*A*) Sampling locations for 78 wild yellowfin tuna, color-coded for the lipid-normalized average concentration (μM) of the 10 previously identified transporter interfering chemicals (Nicklisch et al. 2016). Letters in parenthesis represent subgroups of the sample population with means that were significantly different from each other upon $\log_{10}$-transformation and using Tukey's post hoc analysis. Box and whisker graphs represent the lipid-normalized (*B*) and mass-based (*C*) ranges of concentrations of the P-gp interfering chemicals across the eight capture locations. Note: GOM, Gulf of Mexico; IO, Indian Ocean; NEAO, Northeast Atlantic Ocean; NEPO, Northeast Pacific Ocean; NWAO, Northwest Atlantic Ocean; NWPO, Northwest Pacific Ocean; SWPO, Southwest Pacific Ocean.

Verde Shelf between the late 1950s and early 1970s (Eganhouse and Pontolillo 2008). The second highest levels of OCPs were detected in fish from the NEAO. This site of catch was close to the Canary Islands and, geographically, this archipelago is part of the African continent where DDT is still used to combat proliferation of the Anopheles mosquito that transmits malaria (UNEP 2001; Wandiga 2001). Similarly, the sub-Saharan region in the SEAO had relatively high OCP levels of 3.2 ng/g wet weight, with the DDT group being the most prominent contributor (see Figure S3C). Among all 12 sites, the major contributor to total DDT levels was the metabolite 4,4′-DDE, which is in agreement with previous studies in other fish species (Covaci et al. 2006; Ueno et al. 2002, 2003).

Polybrominated diphenyl ethers. In 1999, about 98% of the global use of Penta-PBDEs was in the United States, including the highly bioaccumulative congeners PBDE-47, -85, -99, -100, -153, and -154 (Hale et al. 2003), five of which are among the nine detected congeners in our survey. Since we measured a less migratory fish species, this could indicate that most of the penta-PBDE congeners produced and used in the United States dispersed globally. Our total PBDE levels ranged from 0.03 to 1.06 ng/g wet weight and were comparable with the average values of the sum of all nine PBDEs in previous studies on U.S. fish samples (Schecter et al. 2006b, 2010c, 2010b). Among PBDEs, the major contributors in the most contaminated sites were PBDE-47 and PBDE-100. This is a similar finding to previous studies, also showing that PBDE-47 is the dominant congener in fish samples (Guo et al. 2008; Hites et al. 2004b; Schecter et al. 2010b). One exception was seen in a fish from the less contaminated site of NWPO, where nearly all the PBDE load was attributed to a single congener, PBDE-209. This is notable because PBDE-209 is not thought to accumulate in organisms due to its

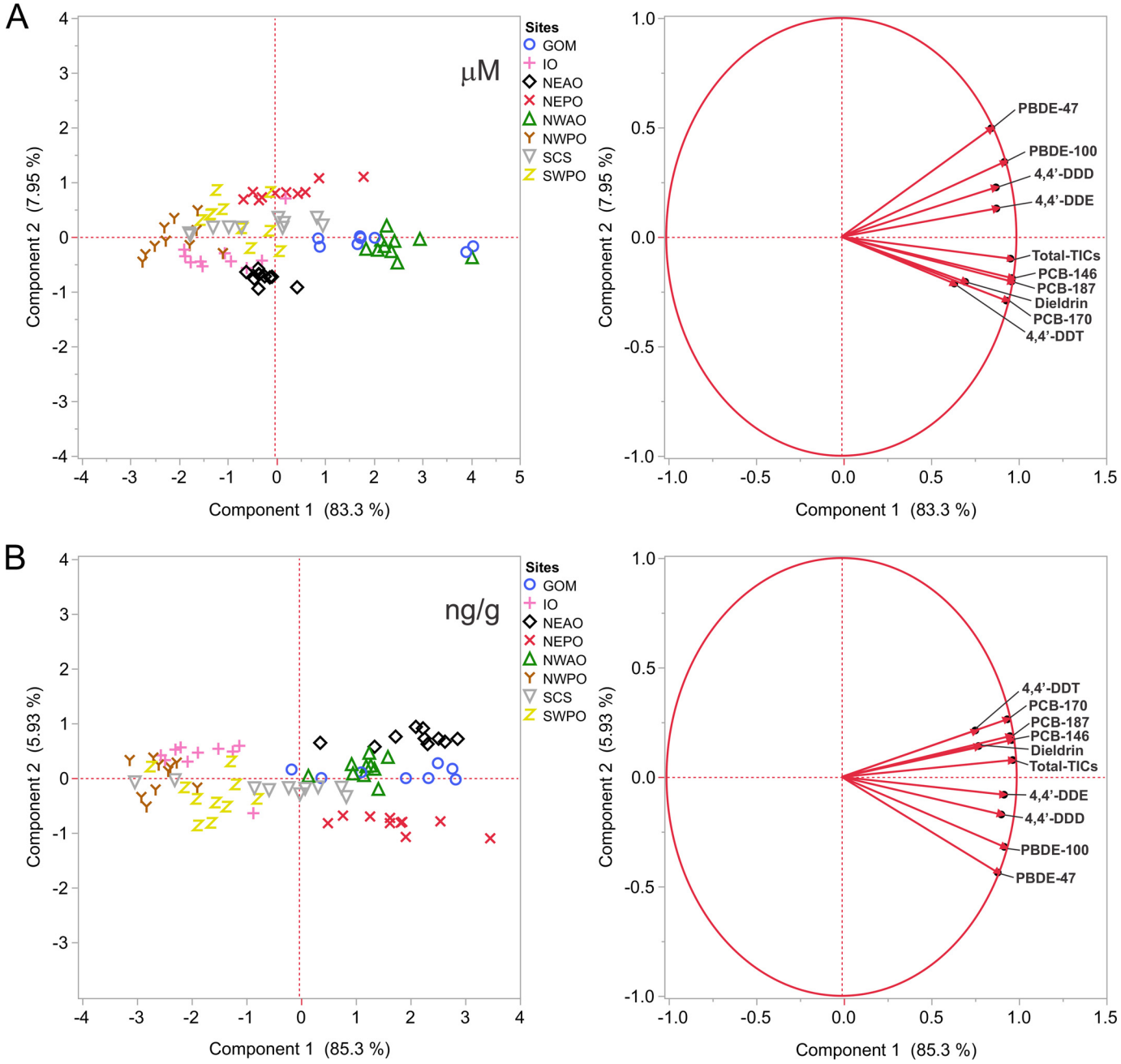

Figure 6. Covariation of individual TICs with the sum of the remaining POPs. Shown are the score (left panel) and loading (right panel) plots from the principal component analysis (PCA) on the TICs detected in tuna and the remaining total POPs (Total-TICs) for all 78 yellowfin tuna. Covariation of each TIC with the remaining POP levels (Total-TICs) could be observed for both lipid-normalized (*A*) and mass-based (*B*) data.

ability to readily metabolize into lower brominated congeners (Guo et al. 2008; Hale et al. 2003; La Guardia et al. 2007).

Polychlorinated biphenyls. We found that the absolute levels of PCBs were highest in the NEAO (~6.5 ng/g wet weight) and the GOM (~ 8.1 ng/g wet weight), the latter possibly being influenced by depositions from the Mississippi River (Santschi et al. 2001; Zhang et al. 2007) and/or atmospheric deposition (Dachs et al. 2002; Lohmann et al. 2007; Lohmann and Belkin 2014). Similarly, despite being banned in most of Europe since 1985 (European Communities 1985), PCB levels in fish tissue and eggs of the North and Baltic Seas are still high (Fliedner et al. 2012; Karl and Lahrssen-Wiederholt 2009), possibly explaining the high levels in the NEAO. Indeed, more recent studies in mammals and birds near the Canary Islands support our data from the NEAO, showing that PCB levels in local species are high (García-Alvarez et al. 2014; Luzardo et al. 2014).

To our knowledge this study is the first to examine all 209 PCB congeners in a large number of capture location controlled fish samples. Most previous studies on PCB levels in fish and seafood determined only a limited amount of individual PCB congeners or the sum of them (Bocio et al. 2007; Domingo and Bocio 2007; Sagratini et al. 2008; Shen et al. 2009; Storelli et al. 2003, 2008; Weijs et al. 2010). Our study revealed that among PCBs, the groups of hexa- and hepta-chlorinated PCBs had the

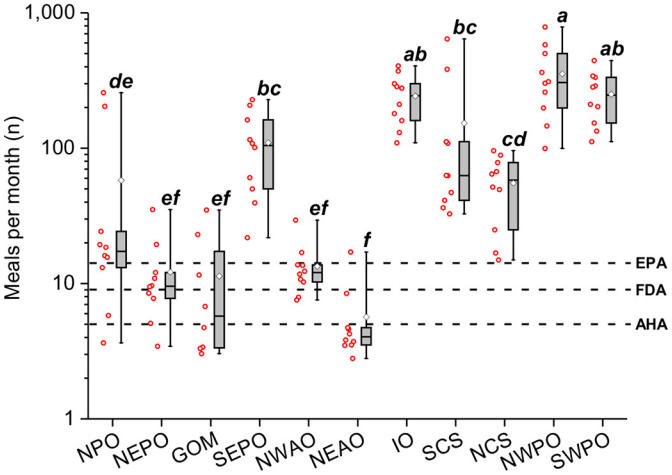

Figure 7. Impact of geographic variation on risk-based fish consumption advisories. Ranges of risk-based consumption limits for 11 sites, calculated in meals per month and based on multiple contaminant exposure with cancerogenic health endpoints, including total PCBs ($n = 209$), toxaphene and dieldrin. The red hollow spheres to the left of each box plot display the individual fish values. Letters in parenthesis represent subgroups of the sample population with means that were significantly different from each other using Tukey's post hoc analysis. The U.S. Food and Drug Administration (FDA) and American Heart Association (AHA) recommended minimum monthly fish consumption levels and the U.S. Environmental Protection Agency (EPA) threshold for unrestricted (>16) fish meals per month are shown as dashed lines. Note: GOM, Gulf of Mexico,IO, Indian Ocean; NCS, North China Sea; NEAO, Northeast Atlantic Ocean; NEPO, Northeast Pacific Ocean; NPO, Northern Pacific Ocean; NWAO, Northwest Atlantic Ocean; NWPO, Northwest Pacific Ocean; SCS, South China Sea; SEPO, Southeast Pacific Ocean; SWPO, Southwest Pacific Ocean.

highest relative contribution across all sites, in agreement with former studies in other fish species (Batang et al. 2016; Covaci et al. 2006; Storelli et al. 2012; Ueno et al. 2003). In addition, the pattern of polychlorinated congeners almost follows a normal distribution, despite the fact that these congeners had different ratios in the commercial Aroclor mixtures (ATSDR 2000; Frame et al. 1996). This might indicate that penta- (PCB-82 to -127), hexa- (PCB-126 to -169), and hepta-chlorinated (PCB-170 to -193) PCBs are more accumulative than lower chlorinated PCBs, including tetra-, tri-, di-, and mono-chlorinated compounds.

Health Effects of Pollutants in Fish

Many POPs examined in our study have well known acute and chronic toxic effects. We investigated three distinct chemical classes of POPs, with organochlorine pesticides (OCPs) being the most heterogeneous class in terms of their chemical structures, properties, and commercial application. Exposure to the OC pesticide DDT has been linked to a variety of adverse human health effects (Rogan and Chen 2005). Acute exposure to DDT can cause seizures and tremors (Costa et al. 2008), whereas long term exposures to DDT can induce liver and breast cancer (Cohn et al. 2007; Persson et al. 2012). In addition, reproductive and developmental defects have been reported for long term exposure to DDT and its metabolites DDE and DDD, including reduced fertility (Cocco et al. 2005), reduced duration of lactation (Karmaus et al. 2005), and reduced birth weight (Longnecker et al. 2001).

The other two classes of POPs investigated in this study, PBDEs and PCBs, belong to the group of poly halogenated compounds. Their structural similarity to the thyroid hormones triiodothyronine (T3) and thyroxine (T4) is thought to be responsible for their pronounced endocrine-disrupting effects, causing developmental, neurological, and behavioral alternations in humans (Boas et al. 2006, 2012; Diamanti-Kandarakis et al. 2009). In addition, the 12 PCB congeners with dioxin-like (coplanar) structure (ATSDR 2000) are known to cause a broad range of adverse health effects ranging from simple chloracne to serious reproductive abnormalities and immune deficiencies (Schecter et al. 2006a).

TICs in Yellowfin Tuna

Among the major contributors to the total pollutant levels were the compounds that we previously identified as inhibitors of an important cell defense protein (Nicklisch et al. 2016). Transporters have already been demonstrated to be important proteins in determining the uptake of hydrophobic xenobiotics such as pharmaceuticals into the human body (Ambudkar et al. 1999; International Transporter Consortium et al. 2010; Leslie et al. 2005), and they may be equally important for understanding the behavior of environmental chemicals in humans and other animals (Epel et al. 2008; Kurelec 1992, 1997; Kurth et al. 2015; Smital et al. 2004). The observation that some persistent organic pollutant congeners could act as inhibitors of these proteins suggests that real world pollutant mixtures, containing high levels of TICs, might act to enhance the accumulation of chemicals that would otherwise be eliminated.

In our previous *in vitro* studies, TIC mixtures inhibited human and mouse P-gp at IC_{10} levels of 7 and 6 μM (Nicklisch et al. 2016). To extrapolate these results to the levels observed in fish, we calculated the lipid-normalized levels of the sum of total POPs and the transporter-inhibiting compounds. Notably, among the most contaminated fish, 3 had TIC concentrations in excess of 2.5 μM, and 18 fish were above 0.5 μM, representing 23% of all the fish caught. It is important to note that our results could underestimate total TIC load because the tuna also had many other POPs for which transporter interactions are presently unknown, with total concentrations of 0.92–12.72 μM and because there are other potential TICs that we did not measure in this study (Bain et al. 1997; Bircsak et al. 2013; Dankers et al. 2013; Luckenbach and Epel 2005; Sreeramulu et al. 2007). Thus, these results suggest that there might be a relatively narrow margin of safety for exposure to TICs from highly contaminated fish, particularly in vulnerable populations.

The principal component analysis of the inhibitory POP congeners showed that fish contaminated with any of these single compounds was also likely to have a high overall load in total POPs. The mechanisms for this association are not completely understood. One possibility is that this could simply reflect their co-variation with the other pollutants in the environment. An alternative explanation, related to their effect on P-gp, could be that exposure to these TICs somehow promotes the accumulation or slows the elimination of other POPs (Epel et al. 2008; Kurelec 1997; Smital and Kurelec 1997; Sreeramulu et al. 2007). However, given that most studies to date identify POPs as inhibitors rather than substrates of transporters, it is as yet unclear how these mixture effects would occur. Future studies, to identify environmental substrates, and examine the effect of TIC exposure on substrate uptake, are needed to better answer this question.

Implications of Geographic Variation for Minimizing Human Exposure to Harmful Chemicals through Fish

Regional differences in POP levels could have important implications for efforts to reduce human exposure. Although variation among different species has prompted advisories to limit consumption of certain types of fish, geographic effects within a

species are usually not accounted for in these advisories. Consistent with the differences in total POP levels, we found dramatic differences in the potential consumption limits that might be recommended among sites. Indeed, these differences were greater than those previously reported for farmed versus wild salmon (Hites et al. 2004a). Given that fish consumption has well appreciated health benefits (Cohen et al. 2005), it seems that identifying and designating where wild fish are captured could be an important tool to minimize fish pollutant risks. At present, the United States imports more than half of its total fish supply from other countries (FAO 2014, 2016; NOAA 2014) and fish of different origins can become mixed in the food supply (Jacquet and Pauly 2008; Warner et al. 2013). Our study underscores how traceability through the supply chain, and spatially stratified monitoring of POP levels, are necessary for management of fish pollutant risk.

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