

Dependence of blood indices of selenium and mercury on estimated fish intake in a national survey of British adults

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Abstract

Objective: Contributions of fish and other foods to variance of selenium and mercury status were studied in British adults.

Setting and design: Plasma and red-cell selenium and whole-blood mercury concentrations were measured during the National Diet and Nutrition Survey of Adults aged 19–64 years in mainland Britain, 2000–2001 ($n = 1216$). Food intake was weighed for seven consecutive days, and foods were combined in groups for data analysis. Four subsidiary groups characterised fish intakes: fried white fish, 'other' white fish, shellfish and oily fish.

Results: Geometric means and 5–95% ranges were: for whole-blood mercury, 5.61 (1.30–22.2) nmol l⁻¹; for plasma selenium, 1.09 (0.83–1.43) μ mol l⁻¹; for red-cell selenium, 1.64 (1.14–2.40) μ mol l⁻¹. Twenty-eight per cent had no fish intake recorded during 7 days; the remaining 72% had a median intake of 237 g over the 7-day period, 5–95% range 45–780 g. Total fish intake was strongly and directly correlated with blood mercury, and moderately with red-cell and plasma selenium. Thus, $\sqrt{\text{total fish intake}}$ was correlated with: $\log_e(\text{blood Hg})$, $t = +19.7$; $\log_e(\text{plasma Se})$, $t = +9.8$; and $\log_e(\text{red-cell Se})$, $t = +9.6$, all $P < 0.0001$. All three biochemical (mercury and selenium) indices were strongly correlated with oily fish intake, and moderately correlated with shellfish and 'other' (= non-fried) white fish, but none was significantly correlated with fried white fish. Blood mercury was strongly and directly correlated with red-cell and plasma selenium, and both increased with age.

Conclusions: Dietary fish, especially oily fish, is a strong predictor of blood mercury and selenium in British adults.

Keywords
Selenium
Mercury
Fish
Survey
British adults

Dietary fish provide a rich source of the essential element selenium¹. Dietary selenium sources have declined recently in the UK, accompanying declining grain imports from selenium-rich North America². Fish, especially oily fish, provide essential $n-3$ fatty acids and other valuable nutrients. However, they also concentrate some potentially toxic substances, especially those that readily cross membranes. One is mercury, converted from inorganic forms to methylmercury chloride by marine bacteria^{3–5}. Inorganic mercury may be present in the human body in the form of mercury amalgam fillings in teeth, and small quantities of this mercury may be released into the circulation (mainly into the plasma). Mercury has no known beneficial functions in the human body, but at toxic levels can cause long-term damage to the developing (foetal) brain, after crossing the placental and blood–brain barriers, and can cause congenital malformations, kidney damage and immune system malfunction⁶.

Fish contribute, on average, about one-third of the British population's total dietary intake of mercury, which

amounts to about 3 μ g daily for an average British adult⁷. Most of the mercury in fish occurs as methylmercury cysteine⁸, which may be converted to methylmercury chloride in the human stomach and then back to the cysteine-bound form in tissues such as red cells, into which it is transferred and concentrated from the plasma and where it becomes bound to the cysteine side-chains of haemoglobin. Most of the mercury in blood (~95%) is located within the red cells and is derived from the organic forms of mercury that predominate in food. In contrast, selenium is distributed about 60%:40% between the red cells and the plasma, and is present both in selenoproteins with genetically encoded selenium and in selenomethionine which is coded by the methionine codon, and thus randomly replaces methionine in all proteins. Haemoglobin contains a major proportion of red-cell selenium, which is mainly in the form of bound selenomethionine⁹.

Selenium and mercury have long been known to interact chemically with each other in various ways, both *in vitro* and within the body, and many studies during

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the past three or four decades have reported a strong direct relationship between the biochemical indices of mercury accumulation and those of selenium status within the human (and animal) body^{10,11}. However, the significance of this interaction for the detoxification and removal of mercury from the body is not well understood¹², and it probably involves a number of different processes. When entering the body mainly from food sources such as fish (rather than from inorganic sources such as industrial mercury exposure or dental amalgam), most of the mercury that enters and remains in the bloodstream is in the red cells, where it binds to haemoglobin as a methylmercury–cysteine side-chain complex^{4,8}. The interaction of organic forms of mercury with selenium and its compounds is less well understood than the interaction that occurs between inorganic mercury and selenium, and requires further study.

In 2000–2001, the National Diet and Nutrition Survey (NDNS) of people aged 19–64 years was performed in mainland Britain. It represented the adult age group (exclusive of pregnant and breast-feeding women) in a rolling series of national surveys that spanned age ranges from 1.5 years to 85+ years. The respondents who were invited to participate in each NDNS were selected to be, as far as possible, representative of the British population. The procedures in the adults' survey included a seven-consecutive-day weighed food intake record and a non-fasting blood sample for a range of biochemical status analyses, including selenium and mercury. The survey objectives and methods, and main outcomes, are described in five survey reports published by The Stationery Office^{13–17}. The estimated mean consumption of white fish by British adults from the NDNS¹³ was 103 g week⁻¹, and of oily fish, 50 g week⁻¹. For fish consumers, the mean values were 221 and 194 g week⁻¹, respectively. The purpose of the present study was to examine the relationships between estimated food intakes and mercury and selenium indices in the survey participants, to test the hypothesis that fish intakes are major contributors to these elements, in a population that includes women of childbearing age.

Methods

The main survey procedures are described in the published survey reports^{13–17}, so only a brief summary is included here. The population sample was obtained by random selection of eligible individuals living in 152 randomly chosen postcode sectors, which were randomly allocated to four sequential 3-month 'rounds' of fieldwork, beginning in July 2000. Participation was invited but not compulsory and partial participation was possible. The survey included a demographic/socio-economic/lifestyle questionnaire, a weighed dietary record kept for seven consecutive days, and a non-fasting blood sample taken by a trained phlebotomist in the participants' home. Three

sub-samples of blood were distributed and used for a wide range of biochemical status measurements. For trace element analysis, containers containing ethylenediamine-*N,N,N',N'*-tetraacetic acid (EDTA) were used. Permission was given for the survey procedures by a Multi-centre Research Ethics Committee and by individual National Health Service Local Research Ethics Committees representing each of the participating postcode sectors.

Trained interviewers assisted the respondents to keep weighed records of intakes of all foods eaten at home, plus diary records of foods eaten outside the home, for seven consecutive days. These records included dietary supplements, information about brands of manufactured foods, methods of food preparation, and leftovers. Computer and face-to-face checks for completeness and consistency were performed. The interviewers allocated the food items to about 6000 food codes, each code being allocated to one of 106 subsidiary food groups, which were in turn aggregated into 57 main food groups and then into 11 major food types. For the present study, the 106 subsidiary food groups provided the basis for analysis of food choices. There were four categories of fish intake within the 106 subsidiary food groups: fried white fish, other white fish, shellfish, and oily fish. We refer to the sum of these four categories as total fish intake.

All three blood indices that are considered in the present study (i.e. concentrations of whole-blood Hg, plasma Se and red-cell Se) were measured in the SAS Trace Element Unit of the University of Southampton at Southampton General Hospital. The EDTA-stabilised blood samples were sent by first-class post to the analytical laboratory, where part of each sample was centrifuged to yield plasma, and this, together with the residue of whole blood, was stored frozen.

For the selenium assays, 100 µl samples of blood plasma and of whole blood were each diluted with 14 volumes of an aqueous solution containing 1% v/v butan-1-ol, 0.66% v/v Triton X-100, 0.01 M ammonium hydroxide, 0.2 mM diammonium dihydrogen EDTA and 2 mM ammonium dihydrogen phosphate¹⁸. ⁷⁸Se, the second major natural isotope of selenium (23.8% natural abundance), was quantified by inductively coupled plasma–mass spectrometry (ICP-MS). The choice of diluent ensured negligible interference from argon adducts. Matrix-matched bovine serum containing selenium standards were used for calibration. In the assays of plasma selenium, internal quality control (ICQ) was achieved by using bovine sera with Se added at 0, 0.4 and 1.6 µM. Nycomed Seronorm quality control samples with assigned values were used for accuracy verification. Participation in UK TEQAS (Trace Element Quality Assurance Scheme, University of Surrey) and a quality assurance scheme organised by the Centre du Toxicologie de Quebec provided inter-laboratory comparisons. The overall mean coefficient of variance for five different IQC samples, which were included after every tenth duplicate unknown

sample, was 5.3%, and assay drift over the 3-month analysis period was <1.3%. The mean bias between observed and target concentrations for the five ICQ samples was $+0.03 \mu\text{mol l}^{-1}$ ($+2.0 \mu\text{g l}^{-1}$ or $+2.9\%$). The performances in both of the above external quality assurance (EQA) schemes at the time of analysis of the survey samples were excellent, with 85% and 100% of results within inner and outer target limits about median values for all participating laboratories – an acceptable performance is 60% and 80% within these limits. In 2001 there was no Quebec EQA scheme for Se in whole blood, however there was a multi element scheme then being set up, called 'ICP MS Comparison Scheme'. It is now known as 'Quebec multi-element EQA scheme' in which one of the elements was selenium. We participated in this scheme, and this was the source of the 17 EQA results for blood Se in the paragraph after next. IQC was achieved using two samples of whole bovine blood and three certified reference samples of whole blood (Nycomed ref. 404107, 404108 and MR9067). The mean bias between observed and target concentrations for these certified reference materials was $+0.02 \mu\text{mol l}^{-1}$ ($+1.7 \mu\text{g l}^{-1}$ or 1.7%). Red-cell selenium concentrations were calculated from whole-blood and plasma selenium concentrations, together with the haematocrit.

Whole-blood mercury concentrations were measured in the same laboratory and by a similar method¹⁹. Blood samples (100 μl) were diluted with 14 volumes of an aqueous solution of 0.7% Triton X-100, 0.12 M ammonium hydroxide, 0.0005 M diammonium dihydrogen EDTA and 0.005 M ammonium dihydrogen phosphate. Calibration was achieved using matrix-matched standards containing mercury added to bovine blood. IQC was achieved by using laboratory-prepared pools of bovine blood with added mercury. A large sample of bovine blood (containing Hg at $0.1 \mu\text{g l}^{-1}$ or $\sim 5 \text{ nmol l}^{-1}$) was spiked with Hg at three levels. 2.5, 5.0 and $10.0 \mu\text{g l}^{-1}$ (equivalent to ~ 12.5 , 25.0 and $50.0 \text{ nmol Hg l}^{-1}$) to give a total of four pools of IQC blood samples. In addition, accuracy verification was achieved using commercially available Nycomed quality control samples with assigned values to control assays for whole-blood mercury. A set of at least two IQC and/or reference samples was analysed at a frequency of not less than one set per 10 duplicate survey samples. Participation in the EQA scheme organised by the Centre du Toxicologie de Quebec for whole-blood mercury provided inter-laboratory comparisons/external assessment of accuracy of analyses.

The mean biases, i.e. the differences between the mean of the Southampton results and the mean of the target values for samples from the EQA schemes, were as follows: UK TEQAS for serum Se, $-0.05 \mu\text{mol l}^{-1}$ at $1.56 \mu\text{mol l}^{-1}$ (-3.0% , $n = 36$); Quebec EQA for serum Se, $-0.11 \mu\text{mol l}^{-1}$ at $2.08 \mu\text{mol l}^{-1}$ (-5.4% , $n = 27$); Quebec EQA for whole-blood Se, $-0.18 \mu\text{mol l}^{-1}$ at $2.84 \mu\text{mol l}^{-1}$ (-6.4% , $n = 17$); and Quebec EQA for whole-blood Hg, $+0.56 \text{ nmol l}^{-1}$ at 79.6 nmol l^{-1} ($+0.70\%$, $n = 18$). These

performances were assessed as being 'excellent' for serum Se in UK TEQAS and for whole-blood Hg in the Quebec EQA schemes, and 'good' for Se in both serum and blood in the Quebec EQA schemes. The much higher selenium concentrations in serum and blood samples from Quebec EQA reflect the higher concentrations seen in the Canadian population; they were greater than those seen in the UK population and in the EQA samples from UK TEQAS, and were above the usual calibration range.

Statistical methods

Statistical analyses were performed using the DataDesk (Data Descriptions Inc.) statistical programme, and included both univariate and multivariate linear regression. In the survey reports, weighting factor adjustments have been used to correct for the known sociodemographic differences between the composition of the survey sample and the entire (census) population of Great Britain, but these were considered unnecessary for the present study, which mainly considers the cross-sectional comparisons between different indices.

A summary distribution of the blood index values is provided in the fourth survey report¹⁶. All three indices exhibited a positively skewed distribution, and the distribution for mercury was more strongly skewed than the two selenium indices. After \log_e -transformation, all three indices had a normal (Gaussian) distribution as indicated by skewness estimates between -1.0 and $+1.0$. Therefore, all data comparisons for the present study were performed with \log_e -transformed biochemical index values.

The analytical approach to the relationships between the blood indices and the food group intakes was tailored to be compatible with the large number of zero intakes in the 7-day diet records for many of the subsidiary food groups that were of interest. For the intake–status comparisons shown in Tables 1–3, the intake (in g/7 days) of each individual food group was scored as '1' for a zero recorded intake during the 7-day period, and as '2', '3' or '4' for ascending thirds of non-zero intake, these scores being entered into linear regression analysis versus the natural logarithm of the blood indices. For the analysis in Table 4, the square root of the 7-day food group intake for fish groups and non-fish groups was entered into linear regression versus the logarithm of the blood indices (all intake estimates were either 0 or ≥ 1.0). Square-root transformation of the numerical values of the food group intakes was used to reduce any disproportionate contributions to the regressions by high outliers. Square-root transformation was used (1) because many of the estimated intake values were zero, which is incompatible with logarithmic transformation, and (2) there were no values below 1.0; therefore square-root transformation reduced the positive skewness in these datasets. Subdivision of food group intakes into four ascending categories and square-root transformation both yielded similar conclusions with respect to the food intake–blood index relationships.

Table 1 Blood mercury concentrations by defined ranges of fish intake

Categories and scores for fish intake	Range of intakes (g/7 days)	Median intake (g/7 days)	<i>n</i>	Geometric mean blood Hg (nmol l ⁻¹)	<i>t</i> for linear regression
Fried white fish					
1	0	0	800	5.44	1.8
2	0.1–125.0	102	145	5.14	
3	125.1–180.0	170	131	6.53	
4	> 180.0	251	140	6.01	
Other white fish					
1	0	0	1000	5.05	7.7***
2	0.1–133.0	90	71	9.71	
3	133.0–248.0	170	72	7.34	
4	> 248.0	340	73	9.66	
Shellfish					
1	0	0	988	5.02	9.3***
2	0.1–49.0	30	75	7.36	
3	49.1–124.0	75	77	8.67	
4	> 124.0	256	76	10.73	
Oily fish					
1	0	0	665	3.79	19.2***
2	0.1–100.0	59.5	194	6.99	
3	100.1–201.0	140	176	9.05	
4	> 201.0	318	181	11.40	
All fish combined					
1	0	0	344	2.97	18.5***
2	0.1–170.0	100	284	5.49	
3	170.1–335.0	235	300	6.80	
4	> 335.0	475.5	288	9.76	

From the entire survey dataset of food group intakes, each category of fish intake (i.e. fried white fish, other white fish, shellfish, oily fish) was subdivided into zero recorded intake and three ascending thirds of intake, so as to generate a score of 1 to 4 for each food group. The cut-off values for thirds of intakes were calculated from all survey respondents who provided intake data, but only about 73% of these had blood measurements. Although canned tuna may be considered relatively non-oily, it is included in the category 'oily fish' because whole tuna is classified as an oily fish. The linear regressions relate the log_e(blood Hg) values to the fish intake scores for each category of fish, and are adjusted for age and gender.

*** $P < 0.0001$; otherwise not significant ($P > 0.05$).

$P < 0.05$ is used as the cut-off for significant differences except in Table 4, where large numbers of food groups are being compared. Here, food groups are included in the table only if at least one of the three comparisons with the blood indices is significant at $P < 0.005$.

Results

Response rates for participation in each main part of the survey were as follows. From an eligible sample of 3704 individuals, 2% could not be contacted and 37% refused to participate. The dietary interview was thus completed by 2251 (61% of the eligible sample) and the 7-day weighed dietary record was completed by 1724 (47% of the eligible sample). A blood sample was obtained from 1318 subjects (36% of the eligible sample), and measurement of the mercury index plus the two selenium indices was achieved for 1216 subjects (33% of the eligible sample).

In this British adult population sample, the unweighted median values for blood Hg concentration in men increased from 2.3 nmol l⁻¹ in the age group 19–24 years to 6.3 nmol l⁻¹ in the age group 50–64 years, and for women the unweighted median values increased from 4.3 nmol l⁻¹ in 19–24-year-olds to 6.6 nmol l⁻¹ in the 50–64-year-olds¹⁶. The highest observed value was

133 nmol l⁻¹ and 129/1216 (10.6%) of values were > 15 nmol l⁻¹, which has been used as a cut-off below which most non-occupationally exposed subjects should fall²⁰; however no values > 250 nmol l⁻¹, the limit of toxicity, were found. The unweighted median red-cell Se concentration in men varied between 1.40 and 1.59 μmol l⁻¹, and in different age groups of women it varied between 1.68 and 1.76 μmol l⁻¹. The unweighted median plasma Se concentration varied between 1.04 and 1.11 μmol l⁻¹ in the different age–gender groups¹⁶. Both blood Hg and plasma Se (and to a lesser degree, red-cell Se) varied significantly between social class categories, with the lowest values of all three indices in the manual and unskilled categories. For instance, the geometric mean blood Hg concentration (nmol l⁻¹) was 8.3 in social class 1, 7.3 in class 2, 5.4 in class 3.1, 4.8 in class 3.2, 4.2 in class 4 and 3.7 in class 5. Likewise, plasma Se exhibited a regularly decreasing pattern from 1.21 μmol l⁻¹ in class 1 to 1.01 μmol l⁻¹ in class 5.

From the data of the present study, it is clear that whole-blood Hg concentration (Table 1), red-cell Se concentration (Table 2) and plasma Se concentration (Table 2) all exhibited similar patterns of relationship with dietary fish intake. All three indices were significantly and directly correlated with intake of non-fried white fish, shellfish and

Table 2 Red-cell and plasma selenium concentrations by defined ranges of fish intake

Categories and scores for fish intake	Mean red-cell Se ($\mu\text{mol l}^{-1}$)	<i>t</i> for linear regression	Mean plasma Se ($\mu\text{mol l}^{-1}$)	<i>t</i> for linear regression
Fried white fish				
1	1.65	-1.3	1.100	-1.4
2	1.51		1.069	
3	1.66		1.104	
4	1.61		1.074	
Other white fish				
1	1.60	5.2***	1.079	4.5***
2	1.82		1.196	
3	1.70		1.166	
4	1.80		1.127	
Shellfish				
1	1.60	5.9***	1.079	5.7***
2	1.69		1.114	
3	1.80		1.209	
4	1.80		1.149	
Oily fish				
1	1.54	11.2***	1.049	10.8***
2	1.66		1.103	
3	1.77		1.163	
4	1.85		1.190	
All fish combined				
1	1.54	8.2***	1.038	8.8***
2	1.58		1.079	
3	1.65		1.106	
4	1.79		1.166	

From the entire survey dataset of food group intakes, each category of fish intake (i.e. fried white fish, other white fish, shellfish, oily fish) was subdivided into zero recorded intake and three ascending thirds of intake, so as to generate a score of 1 to 4 for each food group. The range of fish intakes, the mean intakes and 'n' for each cell is the same as in Table 1. The linear regressions relate the mean red-cell or plasma selenium values to the fish intake scores, for each category of fish, and are adjusted for age and gender.

*** $P < 0.0001$; otherwise not significant ($P > 0.05$).

oily fish, and with all categories of fish combined, but were not significantly correlated with intake of fried white fish. The strongest correlation, for all three blood indices, was with oily fish intake. The magnitude of the *t*-values

indicates that the correlation between the fish intakes and blood mercury concentration was stronger than between fish intake and either of the indices of selenium status.

Just as the biochemical status indices varied between social class categories, so did fish intake patterns. For instance, the sum of oily fish, shellfish and non-fried white fish was about four-fold greater in social class 1 than it was in social classes 4 and 5 combined.

The data in Table 3 confirm that there was a strong direct relationship between blood mercury concentration and each of the selenium indices, which was significant for all age-gender subgroups except the youngest group of women. The variation in the slope of a plot of $\log_e(\text{blood Hg concentration})$ versus $\log_e(\text{red-cell Se concentration})$ for all subjects combined suggests that the relationship was strongest at the higher concentrations of mercury (and selenium). Thus, the *t*-value for the slope corresponding to values of $\log_e(\text{blood Hg concentration}) > 1.5 \text{ nmol l}^{-1}$ was 9.8, with $P < 0.0001$, whereas the *t*-value for the slope corresponding to values of $\log_e(\text{blood Hg concentration}) \leq 1.5 \text{ nmol l}^{-1}$ was 0.9, $P = 0.4$ (not significant).

Table 4 examines the relationships between the three biochemical indices and 7-day intakes of fish or other selected (non-fish) food group intakes, square-root-transformed. Eleven non-fish food groups were directly correlated with one or more of the biochemical indices and four were inversely correlated. The direction and significance of the relationships between the non-fish food groups and the three biochemical indices were essentially unaffected by including total fish intake in the regression model (not shown). The combination of age and sqrt(all fish) explained 27% of the variance of the mercury index; this was increased to 36.4% by the addition of 27 food groups (all sqrt intakes) which were significantly correlated (directly or inversely) with the mercury index. Some of these food group intakes were themselves

Table 3 Linear regression of $\log_e(\text{blood Hg})$ against $\log_e(\text{red-cell Se})$ and against $\log_e(\text{plasma Se})$, in respondents of the National Diet and Nutrition Survey, subdivided by gender and age group

Gender and age group	Log _e (blood Hg) vs. Log _e (red-cell Se)				Log _e (blood Hg) vs. Log _e (plasma Se)			
	Degrees of freedom	Slope	SE (slope)	<i>t</i>	Degrees of freedom	Slope	SE (slope)	<i>t</i>
Men								
19–24 years	37	0.066	0.023	2.8**	38	0.057	0.016	3.5**
25–34 years	105	0.105	0.021	5.1	105	0.065	0.016	4.1***
35–49 years	221	0.122	0.015	8.0***	225	0.096	0.011	8.7***
50–64 years	178	0.126	0.018	7.2***	181	0.069	0.013	5.5***
All men	550	0.114	0.009	12.5***	558	0.077	0.007	11.6***
Women								
19–24 years	43	0.038	0.021	1.8	44	0.040	0.018	2.2*
25–34 years	144	0.075	0.017	4.4***	145	0.045	0.014	3.3**
35–49 years	269	0.131	0.017	7.8***	277	0.060	0.011	5.4***
50–64 years	195	0.170	0.020	8.6***	199	0.105	0.015	7.0***
All women	660	0.112	0.010	11.6***	674	0.065	0.007	9.3***
All subjects	1212	0.113	0.007	16.9***	1234	0.071	0.005	14.3***

SE – standard error.

For each of these calculations, $\log_e(\text{blood Hg})$ was the dependent variable and the selenium index was an independent variable, adjusted for age. In all cases the relationship was positive (i.e. direct).

*** $P < 0.0001$, ** $P = 0.01–0.0001$, * $P = 0.05–0.01$; otherwise not significant ($P > 0.05$).

Table 4 Linear regression of square-root-transformed food group intakes versus \log_e (blood Hg), \log_e (red-cell Se) and \log_e (plasma Se) concentrations

Food group	Regression vs. \log_e (blood Hg)		Regression vs. \log_e (red-cell Se)		Regression vs. \log_e (plasma Se)	
	<i>t</i>	<i>P</i>	<i>t</i>	<i>P</i>	<i>t</i>	<i>P</i>
Direct correlations – fish						
Fried white fish	1.4	0.15	–2.2	0.03	–1.7	0.10
Other white fish	+8.2	<0.0001	+6.1	<0.0001	+5.7	<0.0001
Shellfish	+8.9	<0.0001	+5.8	<0.0001	+5.1	<0.0001
Oily fish	+19.2	<0.0001	+12.1	<0.0001	+11.4	<0.0001
All fish	+19.7	<0.0001	+9.8	<0.0001	+9.6	<0.0001
Direct correlations – non-fish						
Rice	+6.1	<0.0001	+6.7	<0.0001	+4.4	<0.0001
Other bread	+5.1	<0.0001	+3.1	0.002	+2.4	0.02
Chicken and turkey dishes	+6.5	<0.0001	+2.4	0.01	+3.5	0.0004
Salad	+9.6	<0.0001	+8.0	<0.0001	+7.0	<0.0001
Raw tomatoes	+6.3	<0.0001	+6.5	<0.0001	+5.6	<0.0001
Leafy green vegetables	+5.1	<0.0001	+3.8	0.0001	+4.1	<0.0001
Other vegetables	+7.4	<0.0001	+8.7	<0.0001	+6.7	<0.0001
Apples and pears	+5.1	<0.0001	+4.4	<0.0001	4.7	<0.0001
Bananas	+5.2	<0.0001	+4.0	<0.0001	+4.2	<0.0001
Other fruit	+8.4	<0.0001	+9.8	<0.0001	+8.0	<0.0001
Wine	+8.8	<0.0001	+7.4	<0.0001	+6.5	<0.0001
Inverse correlations						
White bread	–5.3	<0.0001	–4.9	<0.0001	–3.5	0.0004
Whole milk	–6.1	<0.0001	–5.1	<0.0001	–4.0	<0.0001
Potato chips	–5.4	<0.0001	–6.3	<0.0001	–5.5	<0.0001
Sugar	–6.0	<0.0001	–7.0	<0.0001	–7.7	<0.0001

Except for fried white fish, the table records only those relatively strong relationships for which the correlation with the mercury index was significant at $t = \pm 5.0$ or better. The other food groups, which did not meet this criterion, are listed in full in the survey report. These included 11 categories of bread, cakes, sweet puddings and cereal products; nine of dairy products; 12 of butter and different types of fat spreads; two of eggs and egg dishes; 10 of meat products; 14 of fruit and vegetables; four of snacks and confectionery; and 10 of alcoholic and non-alcoholic beverages. The regressions are adjusted for age and gender, and there were 1212 degrees of freedom.

significantly correlated with the intake of non-fried white fish: either directly (+) for salad, leafy green vegetables, other vegetables, fruit juice and wine; or inversely (–) for whole milk, meat pies and potato chips.

As noted above, for both the men and the women in the survey, blood mercury and plasma selenium concentrations increased significantly with increasing age. An ancillary question, therefore, is whether these increases might be at least partly attributable to increasing fish intakes with age. For the women, the highly significant direct linear correlation between age and \log_e (blood Hg), $t = +4.81$, $df = 684$, $P < 0.0001$ became non-significant ($t = +1.6$, $P = 0.12$) when adjusted for $\sqrt{\text{total fish intake}}$. For the men, the highly significant direct linear correlation between age and \log_e (blood Hg), $t = +5.37$, $df = 564$, $P < 0.0001$ became much less significant ($t = +3.05$, $P = 0.002$) when adjusted for $\sqrt{\text{total fish intake}}$.

Of the two selenium status indices, plasma Se was more strongly correlated (directly) with age than was red-cell Se. For men and women respectively, the t -values for \log_e -transformed plasma Se versus age were 4.29 and 4.86 (both $P < 0.0001$), and these fell to 2.55 and 3.27 ($P = 0.01$ and 0.001) when adjusted for $\sqrt{\text{total fish intake}}$. Therefore, although the fish adjustment effect here was considerable, it was less than in the case of mercury.

We also ascertained that whole-blood glutathione peroxidase activity, which was measured during the

survey¹⁶, was moderately strongly correlated with both plasma and red-cell selenium concentrations (t -values of 6.3–7.0 for all subjects), whereas its correlation with the blood mercury index was much weaker ($t = +3.5$). If \log_e (blood Hg) was introduced into the regression of \log_e -transformed plasma or red-cell Se (dependent variable) versus blood glutathione peroxidase (independent), then the partial regression attributable to \log_e (blood Hg) was marginally positive ($t = 0.5$ – 0.7) but was not significant, and was not inverse. Thus the mercury burden, at the levels seen in this survey, did not significantly affect the relationship between selenium status (i.e. its blood levels) and blood glutathione peroxidase activity.

Discussion

Since the median blood Hg concentration in UK adults was only about 5 nmol l^{-1} whereas the median blood Se concentration was about 1300 nmol l^{-1} , the blood Hg concentration was at least two orders of magnitude lower than the blood Se concentration. No individuals had an Hg/Se ratio approaching 1:1. This conclusion seems to be consistent with our observation that blood glutathione peroxidase activity was unaffected by variations in the mercury burden (because any major effect of mercury should have created an inverse relationship whereby high mercury levels would have diminished the peroxidase

activity for any given selenium level, and this was not observed).

Fish clearly provides one of the richer sources of selenium in the human diet^{1,21,22}, although dietary sources of selenium are considerably more diverse than those of mercury, and include cereals and meat. Whereas many studies have found a correlation between fish consumption and selenium status, some have not^{23–25}.

The data in Tables 1 and 2 of the present study are compatible with the prediction that dietary fish makes a major contribution to the intake of both mercury and selenium by British adults, and that the variation between individuals in their intakes and status of these two elements is highly sensitive to differences in fish intake. Regular inclusion of fish in the diet is a characteristic that varies considerably between different individuals and between households. However, not all types of fish were equally predictive of the mercury and selenium indices in this survey. Whereas the intake of oily fish was strongly correlated with all three biochemical indices, the intake of fried white fish was not significantly correlated with any of them. Intakes of 'other' (non-fried) white fish and of shellfish were intermediate in terms of *t*-values for the correlations, but these two fish categories contained far fewer non-zero intake values than the other two, which is partly responsible for their lower *t*-values. Therefore the question arises whether fried white fish differs substantially from oily fish and the other two fish categories in its content of mercury and selenium. Although some of the oily fish that is consumed, such as fresh tuna, is near the top of the marine food chain and has relatively high mercury content, other oily fish such as mackerel, herring and sardines are lower in the food chain and should therefore be less contaminated²². The selenium content of oily fish such as herring and mackerel appears to be similar to that of fish used for fried white fish dishes such as cod, haddock and plaice, although shellfish are reported to have a higher selenium content²². Table 3 confirms the prediction that the mercury and selenium indices are strongly correlated with each other, within the blood of nearly all the age–gender subgroups in the survey and in all subjects combined. A common dietary source of both elements, which is encountered in fish, offers a partial explanation of the correlation of the biochemical indices. In addition to this explanation, selenium can also interact chemically with mercury to form specific complexes that may alter the tissue distribution and chemical properties of both of these elements, which probably helps to reduce the toxicity of mercury. An example of such an interaction known to occur in the bloodstream involves selenoprotein P in plasma, each molecule of which can bind large numbers of complexes that in turn each comprise one atom of Se and one of inorganic Hg. Up to 1000 such units may be bound per molecule of selenoprotein P^{26,27}. Whether there are analogous mercury–selenium complexes that

involve methylmercury and occur within red blood cells is less clear. Nevertheless, several studies have recorded a strong direct relationship between blood (including red-cell) mercury and selenium indices in circumstances where methylmercury from dietary fish is likely to be the major source of mercury exposure^{28–32}. In human kidney samples with a high mercury content, selenium and mercury concentrations were correlated in approximately 1:1 molar ratio, whereas no correlation between the two elements was observed at lower mercury concentrations³³, suggesting that extra selenium may be transferred into the kidney when it is needed so as to form a 1:1 Hg–Se complex. In a number of animal and cell culture model systems, some protection against the damaging effects of methylmercury by selenium compounds has been reported^{34–43}, although the mechanisms and efficacy of selenium as an antidote remains controversial. Selenium may increase mercury accumulation in the brain, even though it can counteract the neurotoxicity of mercury⁴⁴.

The relationships of food groups other than fish to the blood indices of mercury and selenium in the survey are examined in Table 4. The intake of these other food groups was not as strongly correlated as fish, especially oily fish. Some of the non-fish food groups listed in Table 4 are likely to be important dietary sources of selenium, such as chicken and turkey, bread and cereals, but few of them are considered to be significant sources of mercury. Some of the food groups that were directly correlated with the biochemical indices, such as wine and green vegetables, may be consumed regularly as part of meals that include fish, and this suggestion appears to be supported by the observation that these food groups were also correlated with non-fried white fish intakes. One possible explanation might be that whereas a 7-day diet estimate is too short to capture long-term fish use and its contribution to blood mercury with perfect accuracy, certain other food groups which tend to be eaten by those same people who have high intakes of non-fried white fish can also contribute to the prediction of blood mercury, although less strongly than fish intake *per se*. If true, then a longer period of dietary estimation should increase the partial correlation of mercury with fish intake and diminish the relative contribution of the other (related) food items; however, this has yet to be tested. Blood mercury concentrations increased markedly with age over the age range (19–64 years) of the survey. Our observation that the significance of this age trend was reduced drastically by the inclusion of $\sqrt{\text{fish intake}}$ in the model appears to be compatible with the hypothesis that much of the increasing age trend in blood mercury may be the result of a parallel increasing age trend in fish intake, and hence an increasing age trend in the intake of methylmercury from fish. Indeed, if the survey estimates of fish intake had been more precisely reflective of the long-term fish intakes of each survey respondent, then the adjustment effect might have been greater still and could perhaps have accounted

for all of the observed age trend in blood mercury. For plasma selenium, the result of inclusion of $\sqrt{\text{fish intake}}$ had a less dramatic, but nevertheless important, effect on the observed age trend; therefore it seems reasonable to suggest that part, but not all, of the increasing age trend in plasma selenium may be due to an increasing intake of selenium from fish with increasing age.

The published survey reports^{13,16,17} have recorded the fact that those respondents who were receiving certain (income support) state benefits had significantly lower intakes of oily fish and shellfish, and significantly lower status index values for mercury and selenium, than people not receiving these state benefits. Our study has extended this finding by showing that there were highly significant social class differences in both fish intakes and mercury/selenium indices, with the lower intakes and index values being associated with the more manual and less skilled social class categories.

In 1972, a Joint Food and Agriculture Organization of the United Nations/World Health Organization Expert Committee on Food Additives and Contaminants (JECFA) defined a provisional tolerable weekly intake (PTWI) of mercury as $0.3 \text{ mg total Hg week}^{-1}$ for adults, of which not more than 0.2 mg should be methylmercury⁴⁵. This is equivalent to 5 and $3.3 \mu\text{g (kg body weight)}^{-1} \text{ week}^{-1}$ for a 60-kg subject. The $3.3 \mu\text{g kg}^{-1}$ value for methylmercury was again upheld in 1989 and 2000; however, in 2003, an upper limit of $1.6 \mu\text{g kg}^{-1} \text{ week}^{-1}$ was recommended⁴⁶ to ensure that the developing foetus, pregnant women and those about to become pregnant would be adequately protected. The US Environmental Protection Agency (EPA) established a reference dose for methylmercury which is only about one-fifth of the 1972 JECFA PTWI, namely $0.1 \mu\text{g (kg body weight)}^{-1} \text{ day}^{-1}$ ($0.7 \mu\text{g}^{-1} \text{ kg}^{-1} \text{ week}^{-1}$), and this was upheld in 2000 by the National Research Council⁴⁷. The 2003 JECFA PTWI and the EPA reference doses correspond to blood Hg levels of 80 and 35 nmol l^{-1} , respectively. Guidelines from UK Health and Safety Executive²⁰ considered blood Hg levels $> 50 \mu\text{g l}^{-1}$ (250 nmol l^{-1}) to warrant medical intervention, and concluded that blood Hg in non-occupationally exposed individuals should normally fall below $3 \mu\text{g l}^{-1}$ (15 nmol l^{-1}). However, it is clearly desirable that mercury intakes should be minimised. It is claimed that sea-fish are generally less contaminated with mercury than freshwater fish, e.g. in countries such as those of Scandinavia²⁹. Pregnant women and women about to become pregnant are especially at risk, and are currently advised by the British Food Standards Agency to avoid eating certain large, long-lived predatory fish that are at the top of the food chain, including shark, marlin and swordfish, because these species contain relatively high mercury concentrations⁴⁸.

It may be possible to reduce mercury levels in fish still further, e.g. by fish-farming in a clean environment; this appears to be an important public health objective in view

of the many known health benefits of fish consumption, and especially those of oily fish.

Conclusions

In a national survey of British adults no toxic levels of mercury were found, which is reassuring because of the known health benefits of fish, especially oily fish. Total fish intake was strongly correlated with blood indices of mercury and selenium, as was the intake of three subgroups of fish; the strongest correlation being with oily fish. In contrast, fried white fish intake was not significantly related to the blood indices of selenium and mercury status. A chemical interaction between selenium and mercury may further enhance the relationship between these two elements within the human body. There was indirect evidence to suggest that the increase of blood mercury with age may be largely attributable to an increase of fish intake with age. Public health advice to increase dietary fish intakes, especially oily fish, would be made less ambiguous if the mercury content of fish could be reduced. Our conclusion that both selenium and mercury blood indices were strongly dependent on the amount of oily fish intake by British adults suggests that the amount of oily fish intake is especially important in determining our exposure to both of these elements. It therefore appears prudent to (1) select those oily fish that have the most desirable (i.e. lowest) Hg/Se ratio and (2) to pursue policies that are aimed at lowering the Hg/Se ratio in oily fish stocks.

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