Phil Spiller (23)

NFPA
The Food Safety People

NATIONAL FOOD PROCESSORS ASSOCIATION

John R. Cady
President and Chief Executive Officer

1350 I Street, NW
Suite 300
Washington, DC 20005
202-639-5917
Fax: 202-637-8464

September 25, 2000

Mr. Joseph Levitt (202-205-4741)
Director, CFSAN
Food and Drug Administration
Federal Building 8
200 C Street, SW
Room 6815, Mail Stop HFS-001
Washington, DC 20204

Dear Mr. Levitt: Joe

Thank you for agreeing to meet with NFPA and its coalition to discuss issues related to methylmercury (MeHg).

We have prepared the attached paper, which speaks to several issues surrounding this topic. Our purpose for requesting the meeting with you and your staff is to present the relevant science on issues regarding MeHg and the human diet and to engage in a dialogue designed to seek clarification on questions surrounding recent reports that require further explanation.

We look forward to meeting with you on Monday and hereby transmit a copy of our paper, which notes where we stand as to the basis of our position and presentations.

Regards,

John

Copy: Jane Henney, M.D., Commissioner of Food and Drugs-FDA
Mrs. Shirley Watkins, Undersecretary, Food Nutrition & Consumer Services-USDA
Rajen Anand, Ph.D., Executive Director, Center for Nutrition Policy & Promotion-USDA

WASHINGTON, DC
DUBLIN, CA
SEATTLE, WA

EXECUTIVE SUMMARY

Summarized herein are several issues focused on statements arising from the recent National Academy of Sciences report, *Toxicological Effects of Methylmercury*. Details on each of the four issues are elaborated upon in the attached document. This document in total, provides information critical when considering changes in current public policy regarding methylmercury.

Issue: Need for FDA Policy To Be Based on Totality Of The Scientific Data
The NAS Committee did not regard their conclusions as the final word, but rather made numerous recommendations regarding development of meta-analytical models, improvements of data systems, and consideration of non-toxicological issues that are essential for rational formulation of public policy. The Committee made a key recommendation with regard to the public health implications of its work: "*Concurrent with the revision of the RfD, harmonization efforts should be undertaken to establish a common scientific basis for the establishment of exposure guidance and reduce current differences among agencies. Harmonization efforts should address the risk-assessment process and recognize that risk-management efforts reflect the differing mandates and responsibilities of these agencies.*" Industry strongly agrees with this recommendation.

Issue: Need For Up-To-Date Data On Fish Consumption, MeHg Concentrations In Fish, and Biomarkers of Mercury Exposure
The NAS Committee repeatedly emphasized shortcomings in U.S. monitoring data. The industry representatives agreed with the Committee's concerns as well as its recommendations urging use of multiple indicators, including the direct measurement of mercury in hair, rather than relying solely on food-consumption data. NHANES IV is collecting such data for a large sample of U.S. women of childbearing age; the data collected in 1999 will shortly be published in the *Morbidity and Mortality Weekly Report*. These data can and should be used to provide a more reliable estimate of the upper range of exposures of this group than is currently available based on the dietary survey data.

To formulate public policy, the most useful information will be linkage of hair measurements with food-consumption patterns of those with the highest exposures. This information is needed to identify the most effective methods to limit exposures to highly exposed individuals. Such information is being gathered with the 1999 and later hair data in the NHANES IV study, and these data will provide the soundest basis available on which to base evaluations of relationships between dietary intake and mercury body burdens and decisions regarding appropriate interventions.

Issue: Estimated Annual Number of U.S. Newborns At Risk For Adverse Neurodevelopmental Effects From *In Utero* Exposure To Methylmercury
The NAS report states, "Available consumption data and current population and fertility rates indicate that over 60,000 newborns annually might be at risk for adverse neurodevelopmental effects from in utero exposure to MeHg" (p. 273). No further indication is provided regarding the derivation of this estimate. Given the potential for a considerable degree of public alarm

over this figure, the industry representatives strongly urge that the basis for it be thoroughly documented and reviewed.

Issue: Consideration of the Nutritional Benefits of Fish

The industry representatives noted that the NAS Committee—although its assignment was to address the toxicological effects of methylmercury—recognized that seafood cannot be regarded merely as a source of exposure to MeHg. Rather, it is an integral part of the American diet and, as such, plays a key role in the nutritional status of the population. Seafood offers nutritional benefits that, simply put, are not available through alternative foods. Information was provided to FDA regarding the nutritional value of seafood, including its ability to provide high quality protein and several valuable vitamins and minerals in foods generally containing little fat, saturated fat, and cholesterol. Seafood is a uniquely abundant source of taurine, an amino acid of particular importance to the developing fetus. Many nutritionists and public health authorities have recommended that the American public increase its consumption of seafoods in order to obtain higher levels of omega-3 fatty acids—constituents that have been convincingly linked to neural development of the fetus and the infant. Intake of omega-3 fatty acids is believed to continue to play a role in continued neural develop of children after infancy. Further, relationships between intake of fish and of omega-3 fatty acids and several types of positive effects on the cardiovascular system of adults are well established.

Issue: Need for FDA Policy To Be Based on Totality Of The Scientific Data

In the House Appropriations Report for EPA's FY-1999 funding, the Environmental Protection Agency (EPA) was directed to contract with the National Research Council to prepare recommendations on the appropriate reference dose (RfD) for mercury (Hg) exposure.

In the prepublication copy of its report, *Toxicological Effects of Methylmercury*, the Committee on the Toxicological Effects of Methylmercury reviewed the RfD for Hg, identified data gaps, and offered recommendations for future research.

It is important to note that the Committee did not regard their conclusions as the final word, but rather recognized that gaps in the available data from the Faroe, Seychelles, and New Zealand studies introduced uncertainties into the Committee's assessments that could be reduced if additional analyses were conducted. Further, they made numerous recommendations regarding development of meta-analytical models, improvements of data systems, and consideration of non-toxicological issues that are essential for rational formulation of public policy.

The Committee also made a key recommendation with regard to the public health implications of its work: *"Concurrent with the revision of the RfD, harmonization efforts should be undertaken to establish a common scientific basis for the establishment of exposure guidance and reduce current differences among agencies. Harmonization efforts should address the risk-assessment process and recognize that risk-management efforts reflect the differing mandates and responsibilities of these agencies"* (p. 276)

In this paper, we present brief discussions of some of the issues which, in our opinion, need to be addressed by the Food and Drug Administration (FDA) in order to formulate a science-based public policy regarding monitoring of the methylmercury (MeHg)content of fish, setting appropriate defect-action levels, and providing dietary guidance or safety advisories to the U.S. population.

Issue: Need For Up-To-Date Data On Fish Consumption, MeHg Concentrations In Fish, and Biomarkers of Mercury Exposure

The Committee repeatedly emphasized shortcomings in U.S. monitoring data relevant to assessing exposures of the total population and specific population subgroups to mercury. This concern ran though many of the chapters of the report. For example, on p. 30, the Committee noted that, *"Uncertainties in such assessments [i.e., estimates of exposure to MeHg through consumption of fish] include those in recall and recording of intake frequency and portion size, misidentification of the species and consumed, and the outdated and incomplete national database on average MeHg concentrations of different fish species."*

This concern led to three related specific recommendations, as follows:

- *"Exposure assessment of the U.S. population—including those with high fish consumption—is needed to provide a full picture of the distribution of MeHg and total Hg exposure nationally and regionally"* (p. 49).

- *"Data are needed that reliably measure both Hg intake and biomarkers of Hg exposure to clarify the relationship between the different dose metrics. NHANES IV data should be examined when it becomes available to determine it if satisfies those needs"* (p. 114).

- *"There is a critical need for improved characterization of population exposure levels to improve estimates of current exposure, track trends, and identify high-risk subpopulations. Characterization should include improved nutritional and dietary exposure assessment and improved biomonitoring for all population groups"* (p. 276).

We strongly endorse these recommendations. The uncertainties in estimating the distribution of exposure to MeHg are significant, and have many sources:

- Short-term general food-consumption surveys are the basis for the exposure estimates cited in EPA's Mercury Study Report to Congress and in the NAS report. These studies are poorly suited for estimating the distribution of consumption of seafood, and especially of seafood by species and source, due to the infrequency of consumption. The upper end of the exposure distribution is particularly uncertain.

- In any event, food-consumption surveys are subject to errors and uncertainties based on misidentification of the type of fish consumed and of the portion size consumed.

- Data on the MeHg concentration of various fish types are limited and out-of-date.

For these reasons we agree with the Committee's conclusion (p. 112) that, *"Each of the dose metrics—dietary records, cord blood, and hair—provides different exposure information. Use of data from two or more of these metrics will increase the likelihood of uncovering a true dose-response relationship."* Regarding the value of measurement of mercury in hair, such measurements remove the limitations and uncertainties associated with estimating exposure by studies of fish consumption, and can also provide demographic and regional exposure information. The NHANES IV study has collected and is continuing to collect such data for a large sample of U.S. women of childbearing age. We understand that the data collected in 1999 will shortly be published in the *Morbidity and Mortality Weekly Report*. These data can be used to provide a more reliable estimate of the upper range of exposures of this group than is currently available based on the dietary survey data.

For the purpose of formulating public policy regarding seafood defect action levels or consumption advisories, hair measurements alone do not provide information about the food-consumption patterns of those with the highest exposures. This information is needed to identify the most effective methods to limit exposures to highly exposed individuals. Such information is reportedly being gathered with the 1999 and later hair data in the NHANES IV study, and these data will provide the soundest basis available on which to base evaluations of relationships between dietary intake and mercury body burdens and decisions regarding appropriate interventions.

It is important to note that the excellent EPA analysis of MeHg intake from fish, as reported in the agency's 1997 Mercury Study Report to Congress, did not include a commodity contribution analysis. Such an analysis would have estimated the impact of different sources of MeHg at various points of the exposure distribution. Thus, these data cannot be directly used to gauge the probable results of any public-policy action that might affect seafood consumption patterns, particularly the impact of such actions on the pregnant women at the upper percentiles of MeHg exposure. What is required is a set of "what-if" analyses estimating both mean and upper percentiles of MeHg exposure under various scenarios representing potential changes in seafood consumption patterns.

Issue: Estimated Annual Number of U.S. Newborns At Risk For Adverse Neurodevelopmental Effects From *In Utero* Exposure To Methylmercury

As stated in the NAS report: *"To further characterize the risks of MeHg, the committee developed an estimate of the number of children born annually to women most likely to be highly exposed through high fish consumption (highest 5% estimated to consume 100 g per day). Available consumption data and current population and fertility rates indicate that over 60,000 newborns annually might be at risk for adverse neurodevelopmental effects from in utero exposure to MeHg"* (p. 273).

- A source for the estimate of 100 g per day fish at the 95th percentile of intake is not provided, but it is not far from Alan Stern's estimate of 106.8 g/day for women aged 18-40 who consumed fish in a 7 day period, based on a telephone survey of New Jersey residents. In our opinion, it would be preferable to cite EPA's estimate, based on 1989-1991 CSFII data. EPA estimates that the 95th percentile value for fish consumption by U.S. women aged 15-45 is 72 g/day.

- No further explanation is provided of the derivation of the 60,000 estimate, and so it is not clear whether or how the 100 g per day estimate influenced the derivation of the 60,000 figure.

Issue: Committee Observations On The Limitations Of The Three Primary Observational Studies And Requests For Additional Data Analyses

In the NAS report, the Committee observed that gaps in the available data from the Faroe, Seychelles, and New Zealand studies introduced uncertainties into the Committee's assessments that could be reduced if additional analyses were conducted.

The Committee made a specific recommendation that potential inter-examiner effects in the Seychelles study be studied and statistically controlled: *"It would be helpful to obtain more comprehensive nutritional data from all three populations [i.e., the cohorts in the Faroe, Seychelles, and New Zealand studies] as well as single-strand hair analyses to address more effectively the issue of spiking or bolus does. A reanalysis of the 5.5-year SCDS [Seychelles] data controlling statistically for examiner might also be useful" (p. 224).* This reanalysis has been done and the data will be available within a month.

On pp. 213-214, the Committee noted several scales used in the Seychelles study that actually comprise a number of subscales measuring different attributes, and indicated that it would be more informative to report the subscale data as well as the integrated data. This has now been completed and the data are available.

Also on p. 214, the Committee pointed out that, *"A second important difference in the assessment batteries used in the Faroe study and SCDS [Seychelles study] relates to the age of assessment—7 year in the Faroe Islands and 5.5 years of age in the SCDS."* The Committee went on to indicate that it regarded tests administered at age 5.5 as likely to be *"less sensitive in detecting subtle neurotoxic effects"* that those administered later. Data from the administration of tests to the Seychelles study participants at age 9 have now become available.

In a related issue, the Committee noted (p. 214) that the period covering ages 60-72 months, when the Seychelles tests were administered, is one of rapid developmental change, which might obscure subtle differences in function. On p. 220, the Committee suggested that, *"Although it seems unlikely that the difference in approach to controlling for age could account for the discrepancies in the findings of those two studies, it would be of interest to see a re-analysis of the SCDS data using the approach that was used in the Faroe Study."* A re-analysis has been performed as requested and will be available within a month.

The Committee noted that the pattern of MeHg exposure in the Faroe study was quite episodic in nature, resulting from occasional exposure to pilot-whale meat with extremely high concentrations of MeHg, while the Seychelles study was more similar to the U.S. pattern, based on a more regular exposure to fish with much lower levels of MeHg. The NRC report states (p. 215), *"Thus, it is possible that the more episodic exposure pattern in the Faroe Islands, with heavier doses per occasion, has a more adverse impact on neuronal development than the more gradual exposure in the Seychelles."* The report recommends (p. 224) that, *"It would be helpful to obtain more comprehensive nutritional* *data from all three populations as well as single-strand hair analyses to address more effectively the issue of spiking or bolus dose."*

These comments indicate that there are uncertainties regarding the dose measure that best represents health risk from MeHg exposure. This could be important in applying the results from the studies on highly exposed populations to the U.S. population. For example, if developmental effects result from episodic fetal brain exposures above a threshold level, it would be important know what these critical concentrations are and whether they occur in the U.S. population.

Issue: Confounding of Effects of MeHg and PCBs In The Faroe Study

In the NRC report, the Committee discussed at some length the possibility that the Faroe Island study results reflect confounding with PCB exposures. (See especially pp. 220, 242-244.) The reason that this issue is important is that the effects from *in utero* exposures to PCBs that have been reported in the literature are the same as those that are at issue for methylmercury.

Two additional publications have recently become available with information relevant to this issue. The first of these is a report from the Joint FAO/WHO Expert Committee on Food Additives (JECFA), "Safety evaluation of certain food additives and contaminants," WHO Food Additives Series: 44, WHO, Geneva, 2000. This WHO committee included one member of the NRC methylmercury committee. In the section of this report addressing methylmercury, the committee made the following comment with regard to the Faroe Island study:

> *"Because PCBs and persistent organic pollutants are associated with both exposure to methylmercury and child development in this study, and because any confounding effects of PCBs will lead to a false-positive association between exposure to methylmercury and child development, the confounding role of PCBs and persistent organic pollutants should be reassessed in order to determine the role of methylmercury in the adverse effects reported in this study."*

Both the NRC report and the WHO report express reservations about the use of umbilical cord tissue as an exposure measure for PCBs. The NRC Committee wrote: *"In the Faroe study, prenatal PCB exposure was measured in umbilical cord tissue rather than cord blood or maternal blood or milk, as in most previous studies, and specimens were obtained for only half the newborns. Cord-tissue PCB concentration has never been validated in relation to blood or milk concentration, and because cord tissue is lean, it might provide a less reliable indication of total PCB body burden"* (p. 220).

The WHO committee commented *"Thus, umbilical cord appears to be unreliable tissue for measuring exposure to PCBs; however, the effect of expressing PCBs on a whole weight basis on the statistical power of the study is mitigated by the wide variation in PCB concentrations between individuals... The reliability of cord tissue for measuring PCB and persistent organic pollutants needs to be clearly demonstrated."*

Secondly, a presentation was given at the "Dioxin 2000" conference (August 13-17, 2000), *Levels of PCBs and Hydroxylated PCB Metabolites in Blood from Pregnant Faroe Island Women* by B. Fängström, M. Athanasiadou, Å. Bergman, P. Grandjean, and P. Weihe. This study reported the results of measurements of PCB and PCB metabolytes in blood lipids collected from Faroese women in their 32nd week of pregnancy (not the cohort of the original Faroe mercury study). The women were divided into two groups based on reported pilot whale consumption. The "low" group reported 0-1 whale meals per month, while those in the "high" group reported 2-8 meals per month. The study found, in reference to the concentrations of PCBs and hydroxylated PCB metabolites, that, "The results confirm that high exposure levels occur among some Faroese. Thus, the results from the high-exposure group seem to be among the highest reported so far."

These quotations indicate that significant uncertainties remain regarding the relative contributions from methylmercury versus PCBs in the Faroe Islands study.

Issue: Consideration of the Nutritional Benefits of Fish and Some Impacts of Replacement of Fish With Other Foods

To their credit, the members of the Committee—although its assignment was to address the toxicological effects of methylmercury—recognized that seafood cannot be regarded merely as a source of exposure to MeHg. Rather, it is an integral part of the American diet and, as such, plays a role in the nutritional status of the population. Seafood offers nutritional benefits that, simply put, are not available through alternative foods. The importance of taking this fact into account in developing public policy was emphasized by the Committee by placing into the Executive Summary of the report the statement:

> *"Because of the beneficial effects of fish consumption, the long-term goal needs to be a reduction in the concentrations of MeHg in fish rather than a replacement of fish in the diet by other foods. In the interim, the best method of maintaining fish consumption and minimizing Hg exposure is the consumption of fish known to have lower MeHg concentrations"* (p. 7).

This concern was repeated in the body of the report in the form of a specific recommendation: *"Because of the recognized nutritional benefits of diets rich in fish, the best method of maintaining fish consumption and minimizing Hg exposure is the consumption of fish known to have lower MeHg concentrations"* (p. 81).

In examining the nutritional benefits offered by seafood, it is appropriate to review two aspects of seafood's role: first, what specific benefits will be lost or diminished if consumers reduce or eliminate fish in their diets and second, what nutritional consequences will accrue due to increased consumption of the foods that they use to replace fish.

Finfish and shellfish are important constituents in diets of cultures around the world, providing substantial amounts of protein and many vitamins and minerals. Finfish products contain relatively low concentrations of fat, saturated fat, and cholesterol, and consumption of these foods therefore has been promoted by health professionals as part of a heart-healthy diet. In recent years, seafood products have become the focus of intense research as key dietary sources of omega-3 fatty acids and taurine, an amino acid.

Nutrient concentrations in selected fish products are contrasted with those of selected high-protein alternatives in the following tables.

Proximate composition and cholesterol

Nutrient	Units	Tuna, light	Salmon, cooked, dry heat	Flounder, cooked, dry heat	Shrimp, cooked, moist heat	Egg, hard-boiled	Chicken breast, roasted w/o skin	Beef, lean, ground, broiled	Ham, lean (5% fat)
		nutrient concentration/ounce							
Energy	kcal	33	61	33	28	44	47	77	37
Protein	g	7.23	7.74	6.85	5.93	3.57	8.79	7.01	5.49
Total lipid (fat)	g	0.23	3.11	0.43	0.31	3.01	1.01	5.23	1.41
Fatty acids, saturated	g	0.066	0.073	0.103	0.082	0.926	0.286	2.055	0.459
Fatty acids, polyunsaturated	g	0.096	0.198	0.183	0.125	0.401	0.218	0.196	0.136
Cholesterol	mg	8.51	0.23	19.28	120.20	55.28	24.10	24.66	13.32

Data source: U.S. Department of Agriculture, Agricultural Research Service. 1999. USDA Nutrient Database for Standard Reference, Release 13. Nutrient Data Laboratory Home Page, http://www.nal.usda.gov/fnic/foodcomp

As shown in the table, one ounce of light tuna provides 33 kcal, 7.2 g protein, and only 0.2 g lipid. An equal amount of broiled, lean beef provides about the same amount of protein, but over twice the calories (77 kcal) and five times the total fat (5.2 g). Although salmon, a relatively fatty fish, provides 3.1 g of fat per ounce, this fat contains a much lower proportion of saturated fat than does beef or any of the other non-fish alternatives. Tuna and salmon, like all animal products, contain cholesterol, but in concentrations less than half that of lean chicken and beef.

Mineral composition

Nutrient	Units	Tuna, light	Salmon, cooked, dry heat	Flounder, cooked, dry heat	Shrimp, cooked, moist heat	Egg, hard-boiled	Chicken breast, roasted w/o skin	Beef, lean, ground, broiled	Ham, lean (5% fat)
		nutrient concentration/ounce							
Calcium, Ca	mg	3.12	1.98	5.10	11.06	14.18	4.25	3.12	1.98
Iron, Fe	mg	0.43	0.16	0.10	0.88	0.34	0.29	0.60	0.22
Magnesium, Mg	mg	7.65	8.79	16.44	9.64	2.84	8.22	5.95	4.82
Phosphorus, P	mg	46.21	78.25	81.93	38.84	48.76	64.64	44.79	61.80
Potassium, K	mg	67.19	106.31	97.52	51.60	35.72	72.58	85.33	99.23
Sodium, Na	mg	95.82	18.71	29.77	63.50	35.15	20.98	21.83	405.12
Zinc, Zn	mg	0.22	0.14	0.18	0.44	0.30	0.28	1.52	0.55
Copper, Cu	mg	0.01	0.02	0.01	0.05	0.00	0.01	0.02	0.02
Manganese, Mn	mg	0.00	0.01	0.01	0.01	0.01	0.00	0.00	0.01
Selenium, Se	mcg	22.79	10.72	16.50	11.23	8.73	7.82	8.22	4.59

Data source: U.S. Department of Agriculture, Agricultural Research Service. 1999. USDA Nutrient Database for Standard Reference, Release 13. Nutrient Data Laboratory Home Page, http://www.nal.usda.gov/fnic/foodcomp

Fish and fish alternates contain relatively low levels of calcium and most other minerals. While iron concentration is high in beef (0.60 g per ounce), shrimp contains a higher iron concentration (0.88 g per ounce), and the concentration in light tuna (0.43 g per ounce) are higher than that in lean ham (0.22 g per ounce).

Fish products, and particularly tuna products, are excellent sources of selenium, an important dietary antioxidant. Wheat provides a substantial portion of selenium intake on a per capita basis; however, wheat is not a consistent source of selenium throughout all geographic regions, as wheat selenium concentrations are dependent on soil concentrations. Seafood products may be important contributors to selenium intakes in some geographic regions.

In addition to fish's importance as a dietary source of selenium, data from animal studies have shown that organic and inorganic selenium influence MeHg deposition and protect against toxicity (Ganther, 1972). Animal studies have shown that selenium ingestion during gestation may reduce the neurodevelopmental effects following *in utero* exposure to MeHg (for example, Fredriksson et al., 1993).

Vitamin composition

Nutrient	Units	Tuna, light	Salmon, cooked, dry heat	Flounder, cooked, dry heat	Shrimp, cooked, moist heat	Egg, hard-boiled	Chicken breast, roasted w/o skin	Beef, lean, ground, broiled	Ham, lean (5% fat)
		nutrient concentration/ounce							
Vitamin C	mg	0.00	0.00	0.00	0.62	0.00	0.00	0.00	0.00
Thiamin	mg	0.01	0.06	0.02	0.01	0.02	0.02	0.01	0.26
Riboflavin	mg	0.02	0.05	0.03	0.01	0.15	0.03	0.06	0.06
Niacin	mg	3.76	1.89	0.62	0.73	0.02	3.89	1.46	1.37
Pantothenic acid	mg	0.06	0.20	0.16	0.10	0.40	0.27	0.11	0.13
Vitamin B-6	mg	0.10	0.06	0.07	0.04	0.03	0.17	0.07	0.13
Folate	mcg	1.13	1.42	2.61	0.99	12.47	1.13	2.55	1.13
Vitamin B-12	mcg	0.85	1.64	0.71	0.42	0.31	0.10	0.67	0.21
Vitamin A, RE	mcg RE	4.82	17.86	3.12	18.71	158.76	1.70	0.00	0.00
Vitamin E	mg ATE	0.15	0.00	0.54	0.14	47.63	0.08	0.06	0.08

Data source: U.S. Department of Agriculture, Agricultural Research Service, 1999. USDA Nutrient Database for Standard Reference, Release 13. Nutrient Data Laboratory Home Page, http://www.nal.usda.gov/fnic/foodcomp

Finfish, shellfish, and other animal protein products are poor sources of Vitamin C. Fish are good sources of most B-vitamins, in general quite comparable to animal protein alternates. Vitamin B-12, obtainable only from animal protein products, is found in seafood products in relatively large concentrations.

Tuna contains Vitamin B in concentrations greater than those found in lean chicken, beef, or ham. Vitamin E, an antioxidant vitamin, is a nutrient of concern for a number of U.S. subpopulations, with many individuals failing to meet dietary recommendations. In the Northeast U.S., for example, over 20% of respondents in the 1994-96 Continuing Survey of Food Intakes by Individuals failed to achieve 50% of the RDA for Vitamin E (USDA, 1998). Of male and female children ages 1-2 in this region, almost 30% failed to achieve 50% of the RDA for Vitamin E.

Omega-3 Fatty Acids

Nutrient	Units	Tuna, light	Salmon, cooked, dry heat	Flounder, cooked, dry heat	Shrimp, cooked, moist heat	Egg, hard-boiled	Chicken breast, roasted wo/skin	Beef, lean, ground, broiled	Ham, lean (5% fat)
		nutrient concentration/ounce							
EPA 20:05	g	0.013	0.357	0.069	0.048	0.001	0.003	0.000	0.000
DHA 22:06	g	0.063	0.711	0.073	0.041	0.011	0.006	0.000	0.000

Data source: U.S. Department of Agriculture, Agricultural Research Service. 1999. USDA Nutrient Database for Standard Reference, Release 13. Nutrient Data Laboratory Home Page, http://www.nal.usda.gov/fnic/foodcomp

Data on concentrations of the omega-3 fatty acids EPA and DHA in fish and alternates demonstrate the superiority of finfish and shellfish as dietary sources. It must be noted that these fatty acids are not concentrated in vegetable oils; finfish and shellfish truly are unique in providing these important substances.

References Regarding General Nutritional Characteristics

Chang, LW, Gilbert M, Sprecher J. Modification of methylmercury toxicity by vitamin E. Environ. Res. 1978; 17(3): 356-66.

Fredriksson A, Gardlund AT, Bergman K, Oskarsson A, Ohlin B, Danielsson B, Archer T. Effects of maternal dietary supplementation with selenite on the postnatal development of rat offspring exposed to methyl mercury in utero. Pharmacol. Toxicol. 1993; 72(6): 377-382.

Ganther HE, Goudie C, Sunde ML, Kopecky MJ, Wagner P. Selenium: relation to decreased toxicity of methylmercury added to diets containing tuna. Science; 175(26): 1122-1124.

USDA, Food Surveys Research Group. Data Tables: Food and nutrient intakes by individuals in the United States, by region, 1994-96. http://www.barc.usda.gov/bhnrc/foodsurgvey/home.htm, 1998.

Taurine

Taurine is a sulphur-containing amino acid recognized to play a role in several physiological functions, including retinal photoreceptor activity, bile acid conjugation, white blood cell antioxidant activity, pulmonary antioxidant activity, decreased platelet aggregation, and the development of the nervous system. Because taurine is the most abundant free amino acid in the central nervous system (CNS), it has been postulated that taurine plays a role in CNS development.

The human fetus accumulates approximately 50-60 mmol per day of taurine during the last 4 weeks of pregnancy. Thus taurine seems to be of benefit during development, an observation that is underscored by the high concentrations in fetal brain. These transfers are critical in the neonatal period and in early life because of the limited ability of newborns to synthesize taurine de novo. If the exogenous neonatal supply of taurine is limited, depletion of the body pool may occur during the first weeks of life.

The noteworthy relationship between taurine and diet is its absence from vegetable sources and its abundance in animal products, particularly fish and shellfish. Frozen cod contains 40 mg taurine per 100 grams, and canned tuna fish contains over 70 mg taurine per 100 g. This in comparison to beef, liver, and chicken which average 30 mg taurine per 100 g.

Human breast milk contains an average of 50 mg taurine per 100 g. Taurine is added to infant formulas to ensure that infants who are not breast-fed receive an adequate supply of this conditionally indispensable amino acid.

As stated above, breast milk contains an average of 50 mg taurine per 100 g, yet the range varies from as little as 24 mg per 100 g to 85 mg per 100 g depending on the mother's taurine status. As the mother's taurine intake increases, so does the breast milk content of taurine.

References Regarding Taurine
Chen XC, Pan ZL, Liu DS, Han X. Effect of taurine on human fetal neuron cells: Proliferation and differentiation. Adv Exp Med Biol 1998;442:397-403

El Idrissi A, Trenkner E. Growth factors and taurine protect against excitotoxicity by stabilizing calcium homeostasis and energy metabolism. J Neurosci 1999;19(21):9459-68

Gucuyner K, Atalay Y, Aral YZ, Hasanoglu A, Turkyiilmaz C, Biberoglu G. Excitatory amino acids and taurine levels in cerebrospinal fluid of hypoxic ischemic encephalopathy in newborn. Clin Neurol Neurosurg 1999;101(3):171-4

Hamosh M. Breastfeeding: Unraveling the mysteries of mother's milk. Medscape Womens Health 1996;1(9):4

Stipanuk MH. Homocysteine, cysteine, and taurine. In: Modern nutrition in health and disease, 9th ed. Eds: Shils ME, Olson JA, Shike M, Ross AC. 1999; Williams and Wilkins, Baltimore, MD

Omega-3 Fatty Acids
Another specific nutritional benefit provided by fish to a degree unmatched by any other food is its content of long-chain polyunsaturated omega-3 fatty acids. The health benefits of these fatty acids to the developing fetus, the newborn, the child, and the adult have

recently been the subject of a great deal of investigation, although in fact the role of n-3 fatty acids in the human diet has been studied for over 30 years (Connor 2000).

N-3 fatty acids are a structural component of phospholipid membranes in tissues throughout the body, and are essential nutrients from fetal development during pregnancy through adulthood. In the United States, the primary source of two essential n-3 fatty acids, docosahexaenoic acid or DHA, and eicosapentaenoic acid or EPA, is fish or fish oils (Kris-Etherton et al. 2000). Current consumption in the U.S. is well below levels recommended by various agencies, governments, and nutritionists to achieve the recognized beneficial effects. Kris-Etherton and colleagues (2000) specify, that, "increasing fish consumption by 4-fold is one strategy that will facilitate meeting the recommendations that have been made for intake of EPA and DHA."

The following sections detail the recognized health benefits of n-3 fatty acids, particularly DHA, to humans from fetal development through adulthood.

Benefits To the Developing Fetus

There are two critical periods during human growth and development in which n-3 fatty acids are essential: during fetal development and after birth until the biochemical development of the brain and retina is completed (Connor 2000). For the developing fetus, the following beneficial effects are noted.

- DHA is an essential component of the neural and vascular tissues of the brain, including the retina (Neuringer 2000). The source of this DHA to be incorporated into developing fetal tissue is from its mother's diet, primarily oily fish such as tuna, salmon, and other cold-water fish. DHA is selectively transferred through the placenta, that is, more DHA and other fatty acids are taken from the mother's blood into the placenta and fetal circulation to achieve higher concentrations in the fetal tissue than in the mother (Al 2000; Innis 1991).
- The human fetal brain experiences a rapid growth spurt in the third trimester of pregnancy. Pre-term babies, those born before development is completed, have lower levels of DHA in their blood and brains than full-term infants, suggesting lower exposures during a critical window of brain growth and development (Monique 2000; Neuringer et al. 1988, Yamamoto et al. 1987, Sinclair and Crawford 1973, and Galli et al. 1977 as cited in British Nutrition Foundation 1992).

Benefits To Infants

Infants and young children continue to have rapid development of brain and vascular tissues after birth (post-natal), and thus continue to need DHA in particular, as well as other n-3 fatty acids. The following beneficial effects are noted for infants, particularly infants that are breast-fed. Note that it remains a critical question for the scientific and regulatory community to determine the kinds of n-3 fatty acids that should be included in infant formulas (Connor 2000).

- For a breast-fed infant, a mother's diet high in DHA promotes high DHA levels in breast milk (Chappell et al. 1985; Finley et al. 1985; Harris et al. 1984; Harzer et al. 1984; Innis et al. 1988; Sanders et al. 1978).
- The biosynthesis of DHA from ∀-linolenic acid (ALA) consists of a series of chain desaturation and elongation reactions at the carboxyl terminal. In infants who are breast fed, the essential fatty acid metabolism is based on the direct supply of long chain polyunsaturated fatty acids bypassing the regulatory desaturation step. Earlier studies on n-3 fatty acids requirements of newborn infants suggest that the activity of the enzymes, particularly desaturase, were low during the newborn period. In addition, the effects of DHA are not replicated by providing equivalent amount of ALA because there appears to be inadequate conversion of ALA to DHA in infants. The synthesis of DHA from ALA may be reduced due to the inhibition of the desaturase enzyme by an excess of ALA.
- In several studies, pre-term infants whose diets were supplemented with DHA (and other fatty acids) had greater improvement in visual and cognitive function. These findings have also been found in term infants (Hoffman et al. 1993; Uauy et al. 1994; Birch et al. 2000).

<u>Benefits to Children</u>

Young children continue to develop neurologic and vascular tissues after infancy. Benefits to children from n-3 fatty acids is an area of active research, but specific effects are less well established than for the developing fetus and in infants. Possible roles of DHA in childhood function include:

- Improvements in dark adaptation and movement skills in dyslexic children (Stordy 2000).
- A possible role in attention-deficit hyperactivity disorder (ADHD) based on findings in several studies in which lower proportions of fatty acids were observed in children with this condition (Burgess et al. 2000).
- An association with reactive airways disease and asthma. Hodge et al. (1996) reported a lower prevalence of airway hyperresponsiveness and wheeze (symptoms of asthma) among Australian children among children who had more frequent consumption of oily fish.

<u>Benefits To Adults</u>

Effects on the cardiovascular system are established benefits to adult consumers of fish containing high levels of omega-3 fatty acids.

- Effects on key risk factors for cardiovascular disease include reductions in triglyceride levels (Nestel 2000; Roche and Gibney 2000) and in heart rate variability (arrhythmia) (Schmidt and Dyerberg 1999; Kang and Leaf 2000).
- In addition, reductions in blood pressure, especially among hypertensive persons, have been noted (Lungershausen et al. 1994; British Nutrition Foundation 1992).
- Separately, epidemiologic studies have shown inverse associations between fish or fish oil consumption and cardiovascular events. Reductions in rates of death, sudden cardiac death (Albert et al. 1998; Daviglus et al. 1997;

Siscovick et al. 1995, 2000; De Logeril et al. 1999; Valagussa et al. 1999), non-fatal heart attacks (myocardial infarction) (Daviglus et al. 1997; Dolecek et al. 1992), and strokes (Dolecek et al. 1992) have all been observed in persons who regularly consume omega-3 fatty acids.

Summary and Conclusions

In summary, the essential role of n-3 fatty acids in the human diet has been studied for several decades. Long-chain polyunsaturated fatty acids are essential nutrients from fetal development during pregnancy through adulthood. During fetal development and infancy, n-3 fatty acids are incorporated into developing neurologic tissues and appear necessary for normal neurologic function. For adults, there are well-studied cardiovascular effects on triglycerides, platelet aggregation, and arrythmias, as well as reductions in cardiovascular morbidity and mortality. Nutritionists from regulatory and other government organizations advise that the U.S. population needs to increase dietary intake of n-3 fatty acids, and that currently, the best source of these nutrients are fish sources.

References Regarding Omega-3 Fatty Acids

Al, M.D.M., A.C. van Houwelingen, and G. Hornstra. 2000. Long-chain polyunsaturated fatty acids, pregnancy, and pregnancy outcomes. *Am. J. Clin. Nutr.* 71(suppl.):285S-91S.

Albert, C.M., C.H. Hennekens, C.J. O'Donnell, U.A. Ajani, V.J. Carey, W.C. Willett, J.N. Ruskin, and J.E. Manson. 1998. Fish consumption and risk of sudden cardiac death. *J. Am. Med. Assoc.* 279:23-28.

Birch, E.E., S. Garfield, D.R. Hoffman, R. Uauy, and D.G. Birch. 2000. A randomized controlled trial of early dietary supply of long-chain polyunsaturated fatty acids and mental development in term infants. *Dev. Med. Child Neurol.* 42:174-181

British Nutrition Foundation. 1992. *Unsaturated Fatty Acids: Nutritional and Physiological Significance.* London: Chapman & Hall.

Burgess, J.R., L. Stevens, W. Zhang, L. Peck. 2000. Long-chain polyunsaturated fatty acids in children with attention-deficit hyperactivity disorder. *Am. J. Clin. Nutr.* 71(suppl):327S-330S.

Chappell, J.E., M.T. Clandinin, and C. Kearney-Volpe. 1985. Trans fatty acids in human milk lipids: influence of maternal diet and weight loss. *Am. J. Clin. Nutr.* 42:29-56.

Connor, W.E. 2000. Importance of n-3 fatty acids in health and disease. *Am. J. Clin Nutr.* 71(suppl):171S-175S.

Crawford, M.A. 2000. Placental delivery of arachidonic and docosahexaenoic acids: implications for the lipid nutrition of pre-term infants. *Am. J. Clin. Nutr.* 71(suppl):275S-84S.

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

de Lorgeril, M., Salen P, J.L. Martin, I. Monjaud, J. Delaye, and N. Mamelle. 1999. Mediterranean diet, traditional risk factors, and the rate of cardiovascular complications after myocardial infarction. *Circulation* 99:779-785.

Dolecek, T.A. 1992. Epidemiological evidence of relationships between dietary polyunsaturated fatty acids and mortality in the Multiple Risk Factor Intervention Trial. *Proc.Soc.Exp.Biol.Med.* 200:177-182.

Finley, D.A., B. Lönnerdal, K.G. Dewey and L.E. Grivetti. 1985. Breast milk composition: fat content and fatty acid composition in vegetarians and non-vegetarians. *Am. J. Clin. Nutr.* 41:787-800.

Harris, W.S., W.E. Connor, and S. Lindsey. 1984. Will dietary ∀-3 fatty acids change the composition of human milk? *Am. J. Clin. Nutr.* 40:780-85.

Harzer, G., I. Dieterich, and M. Haug. 1984. Effects of the diet on the composition of human milk. Ann. Nutr. Metab. 28:231-39.

Hodge, L., C.M. Salome, J.K. Peat, M.M. Haby, W. Xuan, A.J. Woolcock. 1996. Consumption of oily fish and childhood asthma risk. *Med. J. Aust.* 164:137-140.

Hoffman, D.R., E.E. Birch, D.G. Birch, and R.D. Uauy. 1993. Effect of supplementation with n-3 long-chain polyunsaturated fatty acids on retinal and cortical development in premature infants. *Am. J. Clin Nutr.* 57(suppl): 807S-812S.

Innis, S.M., and H.V. Kuhnlein. 1988. Long-chain n-3 fatty acids in breast milk of Inuit women consuming traditional foods. *Early Hum. Dev.* 18:185-89.

Innis, S.M. 1991. Essential fatty acids in growth and development. *Prog. Lipid Res.* 30:39-103.

Kang, J.X. and A. Leaf. 2000. Prevention of fatal cardiac arrhythmias by polyunsaturated fatty acids. *Am. J. Clin. Nutr.* 71(suppl):202S-207S.

Kris-Etherton, P.M., D.S. Taylor, S. Yu-Poth, P.Huth, K. Moriarty, V. Fishcell, R.L. Hargrove, G. Zhao, T.D. Etherton. 2000. Polyunsaturated fatty acids in the food chain in the United States. *Am. J. Clin. Nutr.* 71(suppl):179S-188S.

Lungershausen, Y.K., M.Abbey, P.J. Nestel, P.R.C. Howe. 1996. Reduction of blood pressure and plasma triglycerides by omega-3 fatty acids in treated hypertensives. *J. Hypertension* 12:1041-1045.