

COMMENTS AND RESPONSES

Balancing the Risks and Benefits of Fish Consumption

TO THE EDITOR: I would like to address some misstatements in Jennifer Fisher Wilson's article on the risks and benefits of fish consumption (1). First, the article incorrectly states that methylmercury reaches its highest levels in bottom-feeders, such as crab. Actually, high levels generally occur in long-lived predatory fish, not in bottom-feeders. The U.S. Food and Drug Administration (FDA) and the state of North Carolina recommend that children and women of childbearing age consume crab because of its low reported methylmercury levels (2–4). The FDA collected 59 blue, king, and snow crab samples between 1990 and 2002. The average methylmercury level for these species is 0.06 mg/kg, the same average level reported for pollack, another species recommended by the FDA, U.S. Environmental Protection Agency (EPA), and North Carolina for consumption by children and women of childbearing age (2–4). These levels are well below North Carolina's action level for issuing fish consumption advisories, which is 0.4 mg/kg.

Second, physicians should be made aware of the long list of predatory species that have been reported to have high methylmercury levels (average, ≥ 0.4 mg/kg). Some ocean fish that have been reported to have high methylmercury levels are albacore jack, banded rudderfish, canned white tuna (or albacore tuna), cobia, crevalle jack, greater amberjack, south Atlantic grouper (gag, scamp, red, and snowy), king mackerel, ladyfish, little tunny, marlin, orange roughy, shark, Spanish mackerel, swordfish, tilefish, and tuna (fresh or frozen, not canned light tuna). Some freshwater species have also been reported to have high methylmercury levels in some states, such as blackfish (bowfin), jack fish (chain pickerel), largemouth bass, and warmouth. The average methylmercury levels reported for these fish can be found in Table 1 (4–6).

Third, because fish low in methylmercury are good for the developing brain in children and for the heart in adults, physicians should encourage women of childbearing age (15 to 44 years) and children (younger than age 15 years) to eat at least 2 meals per week of fish low in methylmercury. The FDA, the EPA, and many states, including North Carolina, recommend that women of childbearing age and children eat up to 2 meals a week of fish low in methylmercury (2–4). The general public should be encouraged to eat at least 4 meals a week of fish low in methylmercury (2). Ocean fish that have been reported to have low methylmercury levels or average levels below 0.4 mg/kg are black drum, butterfish, canned light tuna, cod, crab, croaker, flounder, haddock, halibut, herring, jacksnelt, southern kingfish (sea mullet), lobster, mahi-mahi, ocean perch, oysters, pollack, pompano, red drum, scallops, shrimp, speckled trout (or spotted seatrout), sheepshead, skate, spot, tripletail, whitefish, and white grunt (4, 5). Freshwater fish that have been reported to have low methylmercury levels or average levels below 0.4 mg/kg are bluegill sunfish; farm-raised catfish, trout, and crayfish; salmon (canned and fresh or frozen); tilapia; and trout. The average methylmercury levels reported for these fish can be found in Table 2 (4–7).

Fourth, the article incorrectly states that methylmercury is re-

leased mainly through industrial practices, including the burning of fossil fuels and solid wastes. It is the inorganic forms of mercury (for example, elemental mercury and mercuric chloride) that are released from coal-fired power plants, not the organic form of mercury or methylmercury. The inorganic forms of mercury are released from industrial pollution and then eventually are deposited into surface water, accumulating in streams and oceans. Bacteria in the water cause chemical changes that transform the inorganic forms of mercury into methylmercury. It is this organic form of mercury that accumulates in fish and can be toxic. Fish absorb methylmercury from water and their food as they feed on aquatic organisms. Larger, predatory fish accumulate higher concentrations of methylmercury (3, 8).

Fifth, the levels of polychlorinated biphenyls (PCBs) reported in Fisher Wilson's article for farm-raised salmon—30 parts per billion or 0.030 parts per million (ppm) or 0.03 mg/kg—are very low. At this level, the Great Lakes, Connecticut, North Carolina, and other states would not issue a fish consumption advisory. When EPA standard equations are used and a 50% loss from cooking is assumed, a person can safely eat 4 meals per week, which is calculated as follows (9, 10):

$$\begin{aligned} &0.00002 \text{ mg per kg-d (EPA reference dose)} \\ &\times 70 \text{ kg}/0.03 \text{ mg/kg} = 0.046 \text{ kg fish/d} \\ &0.046 \text{ kg of fish/d} \times 30.44 \text{ day/mo} = 1.4 \text{ kg of fish/mo} \\ &1.4 \text{ kg of fish/mo} \times 1 \text{ meal}/0.170 \text{ kg of fish (6-oz meal)} = \\ &\quad 8.2 \text{ meals/mo} \\ &8.2 \text{ meals/mo} \times 2 \text{ (assuming 50\% loss in cooking)} = \\ &\quad 16 \text{ meals/mo} \\ &16 \text{ meals/mo} \times 1 \text{ mo}/4 \text{ wk} = 4 \text{ meals/wk} \end{aligned}$$

Eating 4 meals per week of only farm-raised salmon would be safe, and the PCB exposure dose would be equal to the EPA's recommended dose of 0.00002 mg/kg-d. The cancer risk at this recommended meal limit of 4 meals per week of salmon with average PCB levels of 0.030 ppm would correlate to an excess cancer risk of approximately 1 in 25 000, which is within the EPA target risk range of 1 in 10 000 to 1 in 1 million. The cancer risk can be calculated as shown (9, 10):

$$\begin{aligned} &2.0 \text{ risk per mg/kg-d} \times 0.00002 \text{ mg/kg-d} = \\ &4/100\,000, \text{ or approximately 1 out of 25\,000} \end{aligned}$$

Women of childbearing age and children can safely eat up to 2 meals per week of fish low in PCBs and methylmercury. Eating 2 meals per week of these fish is both safe and healthy.

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Potential Financial Conflicts of Interest: None disclosed.

References

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2. What fish are safe to eat? North Carolina Department of Health and Human Services. Available at www.epi.state.nc.us/epi/fish/whatfisharesafe.pdf.
3. What You Need to Know about Mercury in Fish and Shellfish. March 2004. Environmental Protection Agency. Available at www.epa.gov/waterscience/fishadvice/advice.html.

Table 1. Ocean and Freshwater Fish with High Average Methylmercury Levels or Levels at or above North Carolina's Action Level of 0.4 Part per Million*

| Species | Source | Average Concentration (Samples), ppm (n) |
|---|-------------------|---|
| Ocean fish | | |
| Almaco jack—Florida Atlantic | Florida† | 0.56 (17) |
| Banded rudderfish—Florida Atlantic | Florida† | 0.59 (10) |
| Canned white tuna (albacore) | FDA‡ | 0.358 (170) |
| | Washington State§ | 0.215 (130) |
| Cobia—Florida Atlantic | Florida† | 0.57 (20) |
| | | 1.42 (3) |
| | | 0.41 (2) |
| | | 0.76 (1) |
| Crevalle jack—Florida Atlantic | Florida† | 0.53 (55) |
| Greater amberjack—Florida Atlantic | Florida† | 0.59 (7) |
| | | 0.51 (9) |
| | | 0.46 (41) |
| South Atlantic grouper (snowy, gag, red, and scamp) | Florida† | 0.578 (107)¶ |
| King mackerel, average fork length 34 in | North Carolina** | 0.94 (112) |
| King mackerel, average fork length 40 in | Georgia** | 1.06 (20) |
| King mackerel, average fork length 43 in | South Carolina** | 0.89 (28) |
| Ladyfish—Florida Atlantic | Florida† | 0.72 (30) |
| Little tunny—Florida Atlantic | Florida† | 2.15 (2) |
| | | 0.63 (2) |
| | | 0.79 (6) |
| Marlin | FDA‡ | 0.49 (16) |
| Orange roughy | FDA‡ | 0.54 (26) |
| | | 0.485 (20) |
| Shark, dusky | North Carolina†† | 2.32 (8) |
| Shark, sand tiger | North Carolina†† | 2.95 (2) |
| Shark, sandbar | North Carolina†† | 0.92 (29) |
| Shark, blacktip | North Carolina†† | 0.862 (5) |
| Shark, dogfish | North Carolina†† | 0.67 (3) |
| Shark, hammerhead | North Carolina†† | 1.44 (4) |
| Shark, tiger | North Carolina†† | 1.00 (6) |
| Spanish mackerel—North Carolina Atlantic, average fork length 17 in | North Carolina** | 0.35 (21) |
| Spanish mackerel—South Carolina Atlantic, average fork length 14 in | South Carolina** | 0.2 (73) |
| Spanish mackerel—Florida Atlantic, average fork length 14 in | Florida† | 0.32 (98) |
| Spanish mackerel—Florida Atlantic, average fork length 19 in | Florida† | 0.39 (20) |
| Tilefish | FDA‡ | 1.45 (60) |
| Tuna, fresh/frozen | FDA‡ | 0.38 (131) |
| Blackfin tuna—Florida Atlantic | Florida† | 1.16 (22) |
| Yellowfin tuna —Florida Atlantic | Florida† | 0.30 (33) |
| Freshwater fish | | |
| Blackfish (bowfin) | North Carolina‡‡ | 0.36–1.29 (range of averages reported for 35 counties south and east of Interstate 85, which included 501 samples) |
| Catfish | North Carolina‡‡ | 0.35–1.10 (range of averages reported for 11 counties south and east of Interstate 85, which included 113 samples) |
| Chain pickerel (jackfish) | North Carolina‡‡ | 0.35–1.162 (range of averages reported for 21 counties south and east of Interstate 85, which included 244 samples) |
| Largemouth bass | North Carolina‡‡ | 0.35–1.4 (range of averages reported for 35 counties statewide, which included 1014 samples) |
| Warmouth | North Carolina‡‡ | 0.35–0.62 (range of averages reported for 12 counties south and east of Interstate 85, which included 152 samples) |

* FDA= U.S. Food and Drug Administration; fork length= length from nose to forked tail; ppm= parts per million.

† Reference 5.

‡ Reference 4.

§ Reference 6.

|| Sample is measured in cans.

¶ Including 29 snowy, 67 gag, 9 red, and 2 scamp.

** Analyses of Spanish Mackerel and King Mackerel Caught off the North Carolina, Georgia, and South Carolina Atlantic Coast. Analyzed by North Carolina Division of Water Quality, Georgia Dept. of Natural Resources, and South Carolina Dept. of Health and Environmental Control, November 1998. Unpublished data.

†† 1991–1994 Analyses of Shark Caught off Carteret County Coast and Shark Collected from Ten Processing Plants in North Carolina. North Carolina Division of Water Quality. Unpublished data.

‡‡ Mercury Concentrations in North Carolina Fish Tissue Summarized by County, 1990–2003. Analyzed by North Carolina Division of Water Quality. Unpublished data.

Table 2. Ocean and Freshwater Fish with Low Average Methylmercury Levels or Levels below North Carolina's Action Level of 0.4 Part per Million*

| Species | Source | Average Concentration (Samples), ppm (n) |
|--|----------------------|--|
| Ocean fish | | |
| Black drum—Florida Atlantic | Florida† | 0.14 (36) |
| Butterfish | NMFS | 0.06 (89) |
| Canned light tuna (different species from fresh/frozen tuna) | FDA‡ | 0.12 (131)§ |
| | Washington State | 0.057 (159)§ |
| Cod | FDA‡ | 0.11 (20) |
| Crab | FDA‡ | 0.06 (59) |
| Croaker—Atlantic | FDA‡ | 0.05 (21) |
| | North Carolina¶ | 0.068** |
| | Florida† | 0.06 (21) |
| | Florida† | 0.06 (23) |
| Flounder | Florida† | 0.04 (3) |
| | Florida† | 0.11 (17) |
| Haddock | FDA‡ | 0.03 (4) |
| Halibut | FDA‡ | 0.26 (32) |
| Herring | FDA‡ | 0.04 (38) |
| Jacksmelt | FDA‡ | 0.11 (16) |
| Southern kingfish (sea mullet) | North Carolina¶ | 0.075†† |
| Lobster (spiny) | FDA‡ | 0.09 (9) |
| Mahi-mahi | FDA‡ | 0.17 (3) |
| | FDA‡ | 0.188 (13) |
| | Florida† | 0.11 (130) |
| | Florida† | 0.22 (2) |
| | Florida† | 0.13 (16) |
| | Florida† | 0.12 (24) |
| | South Carolina‡‡ | 0.20 (32) |
| Ocean perch | FDA‡ | Not detected (6) |
| Oysters | FDA‡ | Not detected (34) |
| Pollock | FDA‡ | 0.06 (37) |
| Pompano—Florida Atlantic | Florida† | 0.10 (51) |
| Red drum—Florida Atlantic, total length 18–27 in | Florida§§ | 0.162 (37) |
| Scallops | NMFS | 0.05 (66) |
| Shrimp | FDA‡ | Not detected (24) |
| Speckled trout (or spotted seatrout) | North Carolina¶ | 0.11 (26) |
| Sheepshead | NMFS | 0.13 (59) |
| | Florida† | 0.16 (14) |
| Skate | NMFS | 0.14 (56) |
| Spot | North Carolina¶ | 0.02 (25) |
| | Florida† | 0.12 (21) |
| | Florida† | 0.04 (9) |
| Tripletail—Florida Atlantic | Florida† | 0.13 (74) |
| Whitefish | FDA‡ | 0.07 (25) |
| White grunt—Florida Atlantic | Florida† | 0.27 (15) |
| Freshwater fish | | |
| Bluegill sunfish | North Carolina | 0.03–0.3 (range of averages reported for 54 of 100 counties, which included 341 samples) |
| Farm-raised catfish | Purdue University¶¶¶ | 0.008 (89) |
| | Purdue University¶¶¶ | 0.008 (67) |
| Farm-raised rainbow trout | Purdue University¶¶¶ | 0.009 (34) |
| Farm-raised red swamp crayfish | Purdue University¶¶¶ | 0.025 (70) |
| Salmon, canned | FDA‡ | Not detected (23) |
| Salmon, fresh/frozen | FDA‡ | 0.01 (34) |
| Tilapia | FDA‡ | 0.01 (9) |
| Trout | FDA‡ | 0.03 (17) |

* FDA= U.S. Food and Drug Administration; NMFS = National Marine Fisheries Service; ppm= parts per million.

† Reference 5.

‡ Reference 4.

§ Sample is measured in cans.

|| Reference 6.

¶ North Carolina Methylmercury Marine Fish Tissue Sample Results of Spot, Croaker, Southern Kingfish (Sea Mullet), and Speckled Trout (Spotted Seatrout). October–November 2002. Analyzed by North Carolina Division of Water Quality. Unpublished data.

** 10 composites, 4 fish per composite.

†† 10 composites, 3 fish per composite.

‡‡ Unpublished data (Shelley T. South Carolina Dept. of Health and Environmental Control Personal communication).

§§ Florida Fish and Wildlife Conservation Commission, January 2005. Unpublished data (Henderson G. Personal communication).

||| Mercury Concentrations in North Carolina Fish Tissue Summarized by County, 1990–2003. Analyzed by North Carolina Division of Water Quality. Unpublished data.

¶¶¶ Reference 7.

4. Mercury Levels in Commercial Fish and Shellfish. U.S. Department of Health and Human Services and U.S. Environmental Protection Agency. Available at www.cfsan.fda.gov/~frf/sea-mehg.html.
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TO THE EDITOR: In general, the recent Current Clinical Issues article on the risks and benefits of fish consumption (1) was informative and useful to physicians trying to understand the issues facing their fish-consuming patients. However, as a member of the former National Academy of Sciences/National Research Council committee responsible for the recommendations for exposure to methylmercury referenced in the article, I believe it is necessary to clarify some information regarding the risk to patients with elevated levels of methylmercury.

The article states that “Many Americans are believed to have dangerous levels of methylmercury in their bodies. . . . Levels higher than 5 $\mu\text{g/L}$ in blood or higher than 1 $\mu\text{g/g}$ in hair are potentially hazardous to a developing fetus. . . . This level corresponds to a reference dose of approximately 0.1 $\mu\text{g/kg}$ of body weight per day of methylmercury exposure.” This reference dose is, in fact, specifically defined by the EPA as “an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime” (2). Thus, exposure at the reference dose, and the related blood and hair concentrations of mercury, corresponds to a virtual safe level of exposure. Exposure exceeding this dose exceeds this safety benchmark but does not necessarily imply “danger.” In general, patients who moderately exceed this benchmark, particularly pregnant women and women planning to become pregnant, should be encouraged to reduce their exposure by substituting high-mercury fish in their diets with fish whose mercury levels are characteristically lower. The reference dose is a useful warning sign of elevated exposure and a prompt for prudent modification of a patient’s diet. However, the reference dose should not be interpreted as a bright-line indication of clinical “danger” leading to drastic action on the part of either the physician or the patient.

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Potential Financial Conflicts of Interest: None disclosed.

References

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2. Glossary of IRIS terms: reference dose. Integrated Risk Information System (IRIS). U.S. Environmental Protection Agency. Accessed at www.epa.gov/iriswebp/iris/gloss8.htm#r on 28 March 2005.

Other Disorders That Mimic Infectious Cellulitis

TO THE EDITOR: The review by Falagas and Vergidis (1) is a welcome compilation of many disorders that may be misdiagnosed or confused with infectious cellulitis. I would like to mention 2 additional conditions that are often misdiagnosed as infectious cellulitis.

The first is venous stasis dermatitis, a condition that is preceded by chronic venous insufficiency and is a result of chronic edema and eventual extravasation of erythrocytes into the dermis, leading to signs of inflammation. When this condition ulcerates, secondary infection may occur. However, even when no ulceration exists, the condition may manifest with signs of inflammation, such as pain, erythema, warmth, and induration, although fever is generally not seen unless secondary infection has occurred.

The second is cutaneous expansion syndrome. This condition may result when edema from whatever cause occurs rapidly, expanding and stretching the surface of the skin. Erythema and mild warmth are often present, mimicking mild cellulitis. The lack of fever and the often bilateral occurrence of this disorder are clues against infectious origin.

Either of these conditions may result from venous thrombosis, which the authors discussed, but often occur separately.

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Potential Financial Conflicts of Interest: None disclosed.

Reference

1. Falagas ME, Vergidis PI. Narrative review: diseases that masquerade as infectious cellulitis. *Ann Intern Med*. 2005;142:47-55. [PMID: 15630108]

CLINICAL OBSERVATION

Rhabdomyolysis with Cardiac Involvement and Acute Renal Failure in a Patient Taking Rosuvastatin and Fenofibrate

TO THE EDITOR: *Background:* The 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, or statins, have revolutionized therapy for hypercholesterolemia. Although uncommon, statin-induced myopathy is a well-described side effect (1). A new statin, rosuvastatin, has been particularly scrutinized because rhabdomyolysis and

renal failure occurred in early trials (2). We report on a patient who developed rhabdomyolysis with cardiac involvement and renal failure while taking rosuvastatin.

Case Report: A 67-year-old woman with no history of renal disease was referred with chest pain from an outside institution. She had a history of hypertension, chronic back pain, and hypercholesterolemia and was taking hydrochlorothiazide–olmesartan and oxaprozin. She had been taking rosuvastatin, 10 mg/d, for 9 months; the dose had recently been increased to 20 mg/d with the addition of fenofibrate, 160 mg/d. Two weeks before admission, the patient reported shoulder and chest pains, along with aches in the thigh. A cardiac nuclear perfusion study showed a normal ejection fraction. On the day of admission to our institution, the patient was first transported by ambulance to a local hospital reporting chest discomfort. Cardiac catheterization showed no significant coronary artery disease, a right coronary artery arising from the left coronary cusp, and an ejection fraction of 0.1 with apical dilatation and good contraction of the base, suggestive of an apical ballooning syndrome. The patient had a markedly elevated creatine kinase level (19 000 U/L). She was transferred to our institution for further care.

At our hospital, dopamine and norepinephrine were initially required for blood pressure support. An echocardiogram revealed an ejection fraction of 0.25 with an aneurysmal apex. The Table summarizes clinically significant laboratory findings. Urinalysis showed more than 100 erythrocytes per high-power field and 1 to 3 renal epithelial cells with a urine myoglobin level of 0.069 $\mu\text{g}/\text{mL}$ ($<0.025 \mu\text{g}/\text{mL}$) and proteinuria. Results of a heart biopsy were normal. Before hospital discharge, functional cardiac magnetic resonance imaging revealed an ejection fraction of 0.47 and no perfusion defects. The patient's laboratory values and symptoms progressively improved throughout her hospital stay.

Discussion: Although initially critically ill, our patient recovered with supportive therapy and did not require a balloon pump, ventricular assist device, or hemodialysis. To our knowledge, acute cardiac decompensation with a markedly reduced ejection fraction in the setting of an angiogram negative for coronary artery disease and normal results on right ventricular biopsy has not been previously associated with rosuvastatin. We suspect this incident was either a continuation of the patient's profound myopathy or a consequence of her severe illness. The cause of transient left ventricular apical ballooning syndrome is unknown but seems to be associated with severe emotional or physiologic stress (3).

Our patient's renal failure was probably due to rhabdomyolysis, possibly exacerbated by ischemic acute tubular necrosis due to shock. Mild, poorly defined renal abnormalities (including proteinuria and microscopic hematuria) have been associated with rosuvastatin, particularly at higher doses, as seen in our patient. Fenofibrate is a mild to moderate inhibitor of CYP2C9, and this drug–drug interaction probably contributed to the presumed toxicity of rosuvastatin reported here.

Statin-related side effects involving muscle injury can range from muscular pain to rhabdomyolysis. Cardiac involvement in drug-induced rhabdomyolysis has been reported with propofol and other drugs, including heroin and cocaine (4). Punukollu and colleagues (5) reviewed 91 consecutive patients with rhabdomyolysis and found that 19 (21%) had positive cardiac troponin I values.

Table. Laboratory Values

| Variable | Value in Patient | Reference Value |
|--|------------------|------------------|
| Creatine kinase level, U/L | 13 808 | 38–176 |
| MB fraction, ng/mL | 92 | <6.2 |
| Troponin T level, ng/mL | 1.13 | <0.3 |
| Aldolase level, U/L | 15.8 | <7.4 |
| Myoglobin level, $\mu\text{g}/\text{mL}$ | 6.78 | <0.09 |
| Blood urea nitrogen level, mmol/L (mg/dL) | 20.7 (58) | 2.1–7.5 (6–21) |
| Creatinine concentration, $\mu\text{mol}/\text{L}$ (mg/dL) | 318 (3.6) | 53–106 (0.6–1.2) |
| Thyroid-stimulating hormone level, $\mu\text{IU}/\text{L}$ | 0.49 | 0.3–5.0 |
| Arterial pH | 7.37 | 7.35–7.45 |

Conclusions: Further study is needed to determine whether rosuvastatin has unique cardiac toxicity. Furthermore, additional data are necessary to more clearly define the risks of rosuvastatin, particularly with respect to a possible increased risk for rhabdomyolysis compared with other available statins. Certainly, careful monitoring for adverse effects, such as rhabdomyolysis and acute renal failure, is warranted in all patients treated with this statin.

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Potential Financial Conflicts of Interest: None disclosed.

Reference

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CORRECTION

Correction: Meta-Analysis: Acupuncture for Low Back Pain

In the 19 April 2005 issue, a review on acupuncture for low back pain (1) contained errors. First, in the abstract, the second sentence

of the Data Synthesis section was omitted. It should have read as follows: "The principal measure of effect size was the standardized mean difference, since the trials assessed the same outcome but measured it in various ways." Second, Kelly Forsys, the fourth author, has an MA, not a PhD. Finally, the Table of Contents incorrectly de-

scribed the review as having included 31 randomized trials; it included 33.

Reference

1. Manheimer E, White A, Berman B, Forsys K, Ernst E. Meta-analysis: acupuncture for low back pain. *Ann Intern Med.* 2005;142:651-63. [PMID: 15838072]