

# WORST PILLS



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# BEST PILLS

N E W S

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## The Diabetes Drug Metformin (GLUCOPHAGE) and Lactic Acidosis—A Reminder About a Potentially Fatal Adverse Drug Reaction

**A** communication in the February 2001 issue of the *Australian Adverse Drug Reaction Bulletin* revealed that since the approval of metformin (GLUCOPHAGE) in that country for the treatment of type-2, or adult onset, diabetes mellitus there have been 48 reports of lactic acidosis associated with the use of the drug. Lactic acidosis is the build-up of lactic acid in the blood and it is estimated to be fatal about 50 percent of the time. The result was fatal in 15 of the Australian cases. Of the 48 total cases, known risk factors for the development of lactic acidosis were identified in 35 (73 percent) patients.

The signs of lactic acidosis are:

- feeling very weak, tired, or uncomfortable
- unusual muscle pain

- trouble breathing
- unusual or unexpected stomach discomfort
- feeling cold
- feeling dizzy or lightheaded
- suddenly developing a slow or irregular heartbeat

We initially listed metformin as a *Do Not Use* drug when it came on the U.S. market because of its close chemical similarity to phenformin (DBI, MELTROL), a diabetes drug that was banned in 1977 as an imminent danger after a Health Research Group petition and lawsuit. Phenformin caused hundreds of cases per year of lactic acidosis. It is estimated that metformin causes this adverse reaction about one-seventh as often as phenformin (see the July 1995 issue of *Worst Pills, Best Pills News*).

Our *Do Not Use* recommendation

for metformin was modified with the publication of the United Kingdom Prospective Diabetes Study. This study was the largest and longest ever conducted in patients with type-2 diabetes with a median follow-up of 10 years. In overweight diabetic patients with stable blood sugar levels taking metformin to reach a target blood sugar concentration of 108 milligrams/deciliter, there was a statistically significant decrease in overall mortality, mortality linked to diabetes, and the incidence of a first clinical complication of diabetes. However, in obese patients whose blood sugar was difficult to control there was a statistically significant increase in the number of diabetes-related deaths in those taking older diabetes drugs plus metformin versus those being treated with an older drug alone (see the March

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2000 issue of *Worst Pills, Best Pills News* March 2000).

Metformin was the top selling diabetes drug in the U.S. in 2000, based on retail sales, with over \$1.6 billion being sold.

The Food and Drug Administration (FDA) analyzed reports of lactic acidosis they had received from May 1995, when metformin was introduced in the U.S., through June 30, 1996. The agency had received reports of 47 cases during this period. Of these 47 patients, 43 (91 percent) had one or more risk factors for the development of lactic acidosis. These included pre-existing heart disease or kidney problems, chronic pulmonary disease, severe liver disease and being 80 years of age or older. This analysis was published in the January 22, 1998 issue of the *New England Journal of Medicine*.

We used the FDA's adverse drug reaction database to determine how many reports of lactic acidosis associated with the use of metformin had been received by the agency since the drug was marketed in this country. In addition to the 47 cases the FDA reported in the *New England Journal of Medicine*, we found 157 additional cases reported to the agency through the end of

2000 for a total of 204 reports. The FDA estimates conservatively that only 1 out of 10 serious adverse reactions is ever reported. This would place a more accurate estimate of the number of cases of lactic acidosis with metformin at around 2,000 since the drug was approved in the U.S.

Most troubling is the high percentage of patients with known risk factors for the development of lactic acidosis who were prescribed the drug, 73 percent in Australia and 91 percent of the time in the U.S. cases. The professional product labeling or "package insert" for metformin warns physicians and pharmacists that metformin should not be used in patients:

- with kidney problems;
- with liver problems;
- with heart failure that is treated with medicines, such as digoxin (LANOXIN) or furosemide (LASIX);
- who drink a lot of alcohol. This means binge drinking for short periods or drinking all the time;
- with serious dehydration (have lost a lot of water);
- who are going to have an x-ray procedure with injection of dyes (contrast agents);

- who are going to have surgery;
- who develop a serious condition, such as heart attack, severe infection, or a stroke; and
- who are 80 years of age or older and have not had their kidney function tested.

The FDA has also required that metformin's labeling carry a black box warning. This is the strongest type of warning that the agency can require. The full text of the black box warning appears at the end of this article.

It has become increasingly clear, even to the FDA, that the addition of warnings to a drug's professional product labeling does not protect patients from preventable drug induced injury or death (see story on pg. 52). Unfortunately, patients do not have reliable access to objective risk information about their prescription drugs and are not informed often enough how to recognize the signs of an adverse drug reaction and what steps to take should these signs appear.

#### What You Can Do

You should contact your doctor immediately if you are taking metformin and develop any of the symptoms listed above.

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## Lactic Acidosis

Lactic acidosis is a rare, but serious, metabolic complication that can occur due to metformin accumulation during treatment with GLUCOPHAGE or GLUCOPHAGE XR; when it occurs, it is fatal in approximately 50% of cases. Lactic acidosis may also occur in association with a number of pathophysiologic conditions, including diabetes mellitus, and whenever there is significant tissue hypoperfusion and hypoxemia. Lactic acidosis is characterized by elevated blood lactate levels ( $>5$  mmol/L), decreased blood pH, electrolyte disturbances with an increased anion gap, and an increased lactate/pyruvate ratio. When metformin is implicated as the cause of lactic acidosis, metformin plasma levels  $>5$  g/mL are generally found.

The reported incidence of lactic acidosis in patients receiving metformin hydrochloride is very low (approximately 0.03 cases/1000 patient-years, with approximately 0.015 fatal cases/1000 patient-years). Reported cases have occurred primarily in diabetic patients with significant renal insufficiency, including both intrinsic renal disease and renal hypoperfusion, often in the setting of multiple concomitant medical/surgical problems and multiple concomitant medications. Patients with congestive heart failure requiring pharmacologic management, in particular those with unstable or acute congestive heart failure who are at risk of hypoperfusion and hypoxemia, are at increased risk of lactic acidosis. The risk of lactic acidosis increases with the degree of renal dysfunction and the patient's age. The risk of lactic acidosis may, therefore, be significantly decreased by regular monitoring of renal function in patients taking GLUCOPHAGE or GLUCOPHAGE XR and by use of the minimum effective dose of GLUCOPHAGE or GLUCOPHAGE XR. In particular, treatment of the elderly should be accompanied by careful monitoring of renal function. GLUCOPHAGE or GLUCOPHAGE XR treatment should not be initiated in patients  $\geq 80$  years of age unless measurement of creatinine clearance demonstrates that renal function is not reduced, as these patients are more susceptible to developing lactic acidosis. In addition, GLUCOPHAGE and GLUCOPHAGE XR should be promptly withheld in the presence of any condition associated with hypoxemia, dehydration, or sepsis. Because impaired hepatic function may significantly limit the ability to clear lactate, GLUCOPHAGE and GLUCOPHAGE XR should generally be avoided in patients with clinical or laboratory evidence of hepatic disease. Patients should be cautioned against excessive alcohol intake, either acute or chronic, when taking GLUCOPHAGE or GLUCOPHAGE XR, since alcohol potentiates the effects of metformin hydrochloride on lactate metabolism. In addition, GLUCOPHAGE and GLUCOPHAGE XR should be temporarily discontinued prior to any intravascular radiocontrast study and for any surgical procedure.

The onset of lactic acidosis often is subtle, and accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress. There may be associated hypothermia, hypotension, and resistant bradyarrhythmias with more marked acidosis. The patient and the patient's physician must be aware of the possible importance of such symptoms and the patient should be instructed to notify the physician immediately if they occur.

GLUCOPHAGE and GLUCOPHAGE XR should be withdrawn until the situation is clarified. Serum electrolytes, ketones, blood glucose and, if indicated, blood pH, lactate levels, and even blood metformin levels may be useful. Once a patient is stabilized on any dose level of GLUCOPHAGE or GLUCOPHAGE XR, gastrointestinal symptoms, which are common during initiation of therapy, are unlikely to be drug related. Later occurrence of gastrointestinal symptoms could be due to lactic acidosis or other serious disease. Levels of fasting venous plasma lactate above the upper limit of normal but less than 5 mmol/L in patients taking GLUCOPHAGE or GLUCOPHAGE XR do not necessarily indicate impending lactic acidosis and may be explainable by other mechanisms, such as poorly controlled diabetes or obesity, vigorous physical activity, or technical problems in sample handling.

Lactic acidosis should be suspected in any diabetic patient with metabolic acidosis lacking evidence of ketoacidosis (ketonuria and ketonemia).

Lactic acidosis is a medical emergency that must be treated in a hospital setting. In a patient with lactic acidosis who is taking GLUCOPHAGE or GLUCOPHAGE XR, the drug should be discontinued immediately and general supportive measures promptly instituted. Because metformin hydrochloride is dialyzable (with a clearance of up to 170 mL/min under good hemodynamic conditions), prompt hemodialysis is recommended to correct the acidosis and remove the accumulated metformin. Such management often results in prompt reversal of symptoms and recovery.

# Do Not Use!

## Oral Itraconazole (SPORANOX) or Terbinafine (LAMISIL) for Fungal Nail Infections

The Food and Drug Administration (FDA) issued a public health advisory on May 9, 2001 about the oral anti-fungal drugs itraconazole (SPORANOX) and terbinafine (LAMISIL). Itraconazole has been associated with the development of congestive heart failure and liver toxicity. Liver toxicity has also been seen with terbinafine.

Itraconazole is approved by the FDA to treat serious fungal infections in immunocompromised patients and for finger and toenail fungal infections (onychomycosis) in patients with normal immune systems. Terbinafine is only approved for fungal infections of the finger and toenails.

We listed both drugs as *Do Not Use* for nail fungal infections in our book *Worst Pills, Best Pills* in February 1999.

Both, drugs are heavily promoted directly to consumers with the message that going bare foot to the beach with unsightly toenails due to a fungal infection will cause irreparable harm to one's self-esteem. Toenail fungal infection, in particular, is largely cosmetic and not a medical condition. The promotion for terbinafine has been miraculous. More than \$489 million was spent on terbinafine in this country in 2000.

### Itraconazole (SPORANOX)

The FDA reviewed 94 cases through April 2001 in which itraconazole treated patients developed congestive heart failure. In 58 of the 94 cases, the FDA believes that itraconazole contributed to or may have been the cause of the

congestive heart failure. Death was reported in 13 cases. The FDA also examined 24 cases of liver failure possibly associated with the use of itraconazole, including 11 deaths.

FDA staff, writing in the June 2, 2001 issue of *The Lancet*, more completely described the 58 potential cases of congestive heart failure with itraconazole. The median age

*It is tragic to see people harmed or, even worse, killed from a drug used to treat "unsightly" toenails.*

was 57 years old (the youngest was 15 years old), 65 percent were female and 50 percent were receiving itraconazole for fungal nail infection. Information on the onset of symptoms of congestive heart failure was available for 42 patients. Of these patients, the median onset of symptoms was 10 days after starting the drug and ranged from 1 to 210 days.

The FDA staff carefully described the case of a 60 year old man treated with oral itraconazole for a fungal nail infection. He was not taking any other drugs. Two days after finishing his first course of treatment, he experienced difficulty

breathing and increased weight. He had fluid on his lungs and an enlarged liver. He was treated with a diuretic (water pill) and the symptoms disappeared four days later. A follow-up echocardiogram showed some residual reduction of the heart's pumping action but no underlying structural abnormalities were found. During a second course of itraconazole treatment, the symptoms recurred and were again treated with a diuretic.

### Terbinafine (LAMISIL)

Through April 2001, the FDA has reviewed 16 possible terbinafine associated cases of liver failure, including 11 deaths and two patients who underwent liver transplants. Among those who died of liver failure was a 36 year old male. In addition, there were at least 20 hospitalizations associated with the use of the drug.

The only regulatory action taken by the FDA was to require additional warnings in the professional product labeling or "package insert" for itraconazole and terbinafine. It is irresponsible of the FDA to leave a drug as deadly as terbinafine on the market when its only approved use is for a cosmetic condition.

In addition, the FDA should have withdrawn itraconazole's approval for the treatment of fungal nail infections and required the mandatory distribution of written patient information to increase the likelihood that physicians will not prescribe it for fungal nail infections.

The FDA is fully aware that

*continued on page 53*

# Last Choice Drug—Doxazosin (CARDURA) For High Blood Pressure

**H**ealth Research Group director Dr. Sidney Wolfe presented testimony before the Food and Drug Administration's (FDA) Cardiovascular and Renal Drugs Advisory Committee on May 24, 2001 in support of a citizen petition to warn patients and physicians about the risks of the high blood pressure drug doxazosin (CARDURA) compared to chlorthalidone (HYGROTON), a member of the thiazide family of diuretics or "water pills." Doxazosin

is in the family of blood pressure lowering drugs called alpha-blockers.

Other alpha-blockers currently on the market are prazosin (MINIPRESS), terazosin (HYTRIN), and tamsulosin (FLOMAX). Tamsulosin is only approved to treat the symptoms of benign prostatic hyperplasia (enlarged prostate) and not for high blood pressure.

Doxazosin and chlorthalidone were being compared in one part of the largest clinical trial ever under-

taken known as the Antihypertensive and Lipid Lowering treatment to prevent Heart Attack Trial (ALLHAT). This trial was well designed and enrolled over 43,000 people with high blood pressure. Part of this study was stopped by the National Institutes of Health when patients taking doxazosin were almost twice as likely as those on chlorthalidone to be hospitalized for congestive heart failure, had 25 percent more cardiovascular events,

*continued on page 54*

## **FUNGAL NAIL INFECTIONS,** *from page 52*

changes to a drug's labeling do not protect patients from preventable drug induced injury or death. There is a growing body of published evidence to this effect. Labeling changes not accompanied by FDA mandated patient information are much more likely to fail, as evidenced by the following examples.

- The concurrent use of the withdrawn antihistamine terfenadine (SELDANE) with contraindicated antibiotics and antifungal drugs before and after safety labeling changes and the issuing of "Dear Doctor" letters has been assessed in several studies. A retrospective review of computerized pharmacy claims from a large New England health insurer found that despite significant declines following reports of life-threatening drug interactions and an additional warning in the professional product labeling, concurrent use of terfenadine and contraindicated antibiotics and antifungal drugs continued to occur. Using pharmacy claim data from 1988

through 1994 from state Medicaid programs in Michigan and Ohio, it was found that the concomitant use of ketoconazole (NIZORAL) and erythromycin (EES) with terfenadine had fallen by 80 percent. In a retrospective study of pharmacy claims it was found that coprescription of terfenadine with either erythromycin or ketoconazole continued to occur after regulatory action.

- The FDA reviewed reports of lactic acidosis associated with the use of the diabetes drug metformin (GLUCOPHAGE) occurring from May 1995 through June 30, 1996, the drug's first year on the market in the U.S. Of the 47 patients with a confirmed diagnosis of the adverse drug reaction, 43 (91 percent) had one or more risk factors for lactic acidosis that were listed in the drug's professional product labeling at the time of its approval. In other words, physicians prescribed it to patients who should not have used the drug because of other pre-existing diseases. Lactic acidosis is an adverse drug

reaction that is fatal in about 50 percent of cases. (See also story on page 49.)

- Recently, the effect of June 1998 FDA regulatory actions in the form of a "Dear Doctor" letter and additional safety labeling changes on the contraindicated prescribing of cisapride (PROPULSID) were assessed. At one state Medicaid site surveyed for the study, in the year prior to new warnings about the drug the use of cisapride was contraindicated in 60 percent of those for whom the drug was prescribed. In the year after the regulatory actions, the proportion of contraindicated patients prescribed this drug had only decreased to 58 percent.

It is tragic to see people harmed or, even worse, killed from a drug used to treat "unsightly" toenails caused by a fungus.

### **What You Can Do**

You should not use itraconazole or terbinafine for fungal nail infections.

## DOXAZOSIN, from page 54

and had a significantly elevated risk of stroke.

The complete text of Dr. Wolfe's testimony can be found on our web site at [www.citizen.org/hrg/PUBLICATIONS/1575.htm](http://www.citizen.org/hrg/PUBLICATIONS/1575.htm). Readers without access to the Internet can write to us at Public Citizen Health Research Group, 1600 20<sup>th</sup> Street, NW, Washington, DC, 20001 and request publication #1575.

The doxazosin-chlorthalidone ALLHAT results were published in the April 19, 2000 issue of the *Journal of the American Medical Association*. We warned readers of these results in the May 2000 issue of *Worst Pills, Best Pills News*, urging that alpha-blockers not be used to treat high blood pressure.

The petition emanated from a class action lawsuit filed by the New York firm of Milberg, Weiss, Bershad, Hynes & Lerach against Pfizer, Inc., doxazosin's manufacturer, in the U.S. District Court for the Southern District of New York to require, as one remedy, the emergency notification of physicians and patients about the premature stopping of the doxazosin arm of the ALLHAT study. The U.S. District Court judge instructed the law firm on November 16, 2000 to first petition the FDA.

The citizen petition asked that:

1. the FDA require Pfizer to notify all patients in the U.S. who have taken or are taking Cardura to control their blood pressure and that the FDA issue a press release regarding the interim results of ALLHAT;
2. the FDA require a boxed warning in the professional product labeling or package insert for Cardura and its generic versions informing prescribers of the ALLHAT interim results; and
3. that if deemed necessary by the FDA, additional labeling changes for Cardura be made that may include changes in approved

uses, warnings, precautions, and contraindications.

We supported the fundamental intention of the petition to require

## *Several paternalistic members of the committee held to the worn view that only physicians should tell their patients about doxazosin.*

notification of physicians and patients of the ALLHAT results, although we believe that as it stands it will not achieve the desired goal. Therefore, we urged the committee to make additional recommendations to the FDA:

1. The mandatory distribution by pharmacists of FDA-approved written patient information, known as Medication Guides, notifying patients of the ALLHAT results with each new and refill prescription for doxazosin and the other alpha-blockers.
2. The addition of a black box warning to professional product labeling or "package insert" for all members of the alpha-blocker family to inform physicians and pharmacists of the ALLHAT results.
3. That all alpha-blockers approved by the FDA be relegated, in their labeling and in Medication Guides, to second, if not last line

treatment for high blood pressure.

Much of the advisory committee's debate over the merits of the citizen petition and our recommendations were discouraging from a consumer perspective. Several paternalistic members of the committee held to the worn view that only physicians should tell their patients about doxazosin, rather than alerting patients directly with an FDA-approved Medication Guide. Too many physicians tell their patients little if anything about the risks of prescription drugs to rely on this mechanism alone.

Remarkably, some members of the committee maintained that the evidence from ALLHAT concerning doxazosin was not convincing and the study results should not be included in the drug's professional product labeling. One of the regulatory standards for requiring changes to a drug's labeling is that new information has become available since the drug was approved.

By the time the advisory committee meeting finished, it was difficult to tell if the FDA will take any action on the citizen petition or our recommendations. We can only hope that they do the right thing by informing the public of the ALLHAT results.

### What You Can Do

*Do not discontinue any high blood pressure medication without consulting your physician.*

If you are now using or thinking of using doxazosin or another alpha-blocker alone or as a part of your treatment for high blood pressure you should talk to your physician about alternative treatment.

If you are being treated for high blood pressure and this treatment does not include a water pill you should ask your doctor why not.

# Reduction In Cancer Risk Claim for Antioxidant Vitamins Rejected by the Food and Drug Administration (FDA)

In a 69 page letter to the Washington D.C. law firm Emord & Associates dated May 4, 2001, the Food and Drug Administration's (FDA) Center for Food Safety and Applied Nutrition (CFSAN) rejected the claim that vitamin C- and vitamin E-containing dietary supplements reduced the risk of cancer. Dietary supplement producers wanted to make the explicit claim that "Consumption of antioxidant vitamins may reduce the risk of certain kinds of cancers."

CFSAN is the part of the FDA that must cope with the dangerous Dietary Supplement Health and Education Act (DSHEA) of 1994 that deregulated the supplement industry and left consumers to face a marketplace full of untested and thus potentially dangerous products frequently promoted implicitly, if not explicitly, for unsubstantiated uses. The FDA can prevent supplement producers from making explicit health claims without scientific proof such as cancer prevention. This is about the only regulatory authority that the FDA has over supplements since the passage of DSHEA. However, DSHEA does allow supplement producers to make structure/function claims. For example, a supplement producer can claim that a product promotes prostate health but not that it treats the symptoms of an enlarged prostate gland without scientific proof. Only lawyers can tell the difference between a health and a structure/function claim since structure/function claims are intentionally very deceptive.

CFSAN conclusions were delivered to Emord & Associates because this firm represented dietary supplement producers in a lawsuit

against the FDA on First Amendment grounds when the FDA refused to allow health claims on certain dietary supplements including vitamin C and vitamin E. The U.S. Court of Appeals for the D.C. Circuit had previously held that FDA's decision not to authorize the health claims violated the First Amendment. This was because the agency did not consider whether

*The FDA refused to allow health claims on certain dietary supplements including vitamin C and Vitamin E.*

the claims—which failed to meet the "significant scientific agreement" standard of evidence that the regulations require the FDA to use in evaluating the scientific validity of health claims—could be made "nonmisleading" to consumers by adding a disclaimer to the labeling.

The Code of Federal Regulations requires the FDA to evaluate the scientific validity of claims using the significant scientific agreement standard. Under this standard, the agency may approve a health claim only "when it determines, based on the totality of publicly available scientific evidence (including evidence from well-designed studies conducted in a manner which is consistent with generally

recognized scientific procedures and principles), that there is significant scientific agreement, among experts qualified by scientific training and experience to evaluate such claims, that the claim is supported by such evidence."

CFSAN concluded that "The scientific evidence against a claim relating vitamin C or vitamin E, alone or in combination (i.e., antioxidant vitamins) and reduced risk of certain kinds of cancer or of individual cancers...outweighs the scientific evidence for a claim about such a relationship," and that a claim of benefit for antioxidant vitamins "cannot be qualified in such a way as not to mislead consumers."

The complete text of CFSAN's letter to Emord & Associates can be found on the agency's web site at [www.cfsan.fda.gov/~dms/ds-ltr23.html](http://www.cfsan.fda.gov/~dms/ds-ltr23.html).

The controversy over whether or not vitamin C or vitamin E alone or in combination prevents cancer arises from early studies that showed a benefit for these supplements. These early studies are termed observational or epidemiological studies. In this type of study researchers look retrospectively at two groups of subjects, those with the outcome of interest, cancer in this case, and a comparable group without cancer. The researchers then survey the two groups to determine if there are any differences in their behavior, such as taking vitamins C and E supplements, or life-styles that could account for the development of cancer. There are two major weaknesses of this type of study. First, the researchers must rely on the ability of subjects to recall their behavior. This has pitfalls. Second, observational studies cannot show a

cause and effect relationship between a behavior and the outcome of interest, again cancer in this case.

Observational studies are very useful in generating new ideas about therapeutic interventions but the results of these types of studies can only be validated with experiments. Controlled clinical trials are the experiments that are used to validate or reject the results of observational studies because they can establish a cause and effect relationship. The strongest evidence about the effect of an intervention comes from controlled clinical trials.

We have seen in the past that when a strongly held medical doctrine is tested in a controlled clinical trial it may fail. A recent example of this is the long held belief that postmenopausal estrogen replacement would protect women from cardiovascular disease, a view that was based on observational studies. When subjected to a controlled clinical trial it was found that estrogen replacement therapy did not protect postmenopausal women, in fact, it appeared that there was an increase in cardiovascular events during the first year of treatment (see *Worst Pills, Best Pills News* November 1998).

When CFSAN examined both observational studies and controlled clinical trials, the weight of the

evidence was against the claim that vitamin C or vitamin E prevents cancer. In addition, CFSAN's conclusions were consistent with the National Academy of Sciences' Institute of Medicine's, April 2000 Dietary Reference Intakes report, which found the relationship between vitamin C or vitamin E, selenium and carotenoids (precursors of vitamin A) and the prevention of chronic diseases had not conclusively been proven.

CFSAN cited potential adverse effects associated with the use of high doses of vitamins C and E, including diarrhea and other GI disturbances for vitamin C, and prolonged bleeding time for individuals using vitamin E at the same time as nonsteroidal anti-inflammatory (NSAID) drugs, such as ibuprofen (MOTRIN) or naproxen (ALEVE). Additionally, there were "unexpected increases in the incidence of some cancers" associated with the intake of antioxidant vitamins. The agency referred to a 1994 Chinese study demonstrating an increased prevalence of gastric cancer among subjects receiving dietary supplements containing 120 mg vitamin C and molybdenum. It was not clear that the increased prevalence of gastric cancer resulted from vitamin C consumption, although CFSAN noted, "it cannot be ruled out that vitamin C contrib-

uted to this adverse finding."

CFSAN cited the Alpha-Tocopherol, Beta Carotene (ATBC) clinical trial, done in 1994, that found the incidence of bladder and stomach cancers among subjects receiving vitamin E supplements "was reported to be above the incidence for subjects not supplemented with vitamin E." Additionally the ATBC analyses "presented very mixed results at other cancer sites," with prostate and colorectal cancers appearing to benefit from vitamin E supplementation, while subjects demonstrated an increased risk of bladder and stomach cancers when taking vitamin E.

The dietary supplement industry was founded on and continues to thrive on deceit. Supplement producers trying to invoke their First Amendment right in court to conduct misleading advertising is reprehensible. Without resorting to deception, this industry would not have increased its sales from \$8.8 billion in 1994 (when DSHEA passed) to an estimated \$15.7 billion for 2000, according to the *Nutrition Business Journal*.

### What You Can Do

Your best source of vitamin C and vitamin E is a healthy balanced diet. Remember, there is nothing natural about taking large doses of dietary supplements.