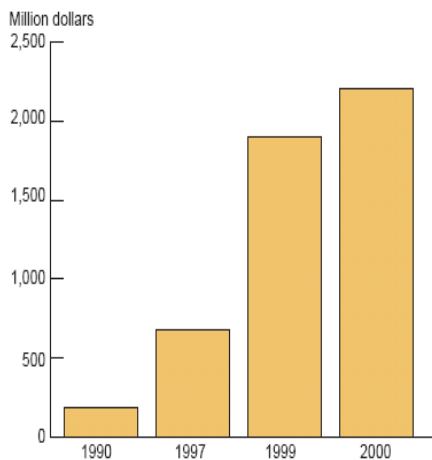


The Evidence behind Organic Food

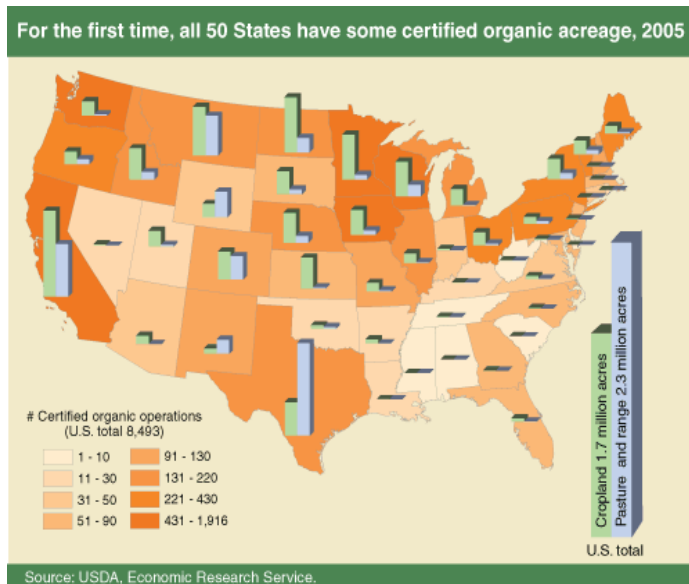
For the vast majority of human history, organic farming was the only option. In the twentieth century, demands from a growing population coupled with a series scientific breakthroughs to rapidly change the face of agriculture in much of the world. While government regulators have attempted to assure that all new technologies are sustainable and safe for humans, a spate of conspicuous failures has led to increased concern about agricultural practices. This concern has given rise to what is popularly known as the “organic movement,” a set of ideas that largely seeks to eliminate synthetic pesticides, herbicides, and antibiotics from agriculture.

Until 2002, there was no legal definition of “organic.” At that time, the United States Department of Agriculture (USDA) promulgated regulations defining what could be marketed as “organic.” The USDA now defines organic food as food “produced by farmers who emphasize the use of renewable resources and conservation of soil and water to enhance environmental quality for future generations.” More specifically, the USDA prohibits (with limited exceptions) the use of antibiotics, growth hormones, conventional pesticides, fertilizers made with synthetic ingredients, bioengineering and ionizing radiation which have been shown to have adverse effects on the environment.¹

Figure 3—Sales of organic fruits and vegetables: 1990, 1997, 1999, and 2000



Source: 1997 data, Food Industrial Management Program at Cornell University; 1999, 2000, *Nutrition Business Journal*.



Consumption of organic food has increased substantially in recent years. The most common reasons people cite for buying organic food are: 1) no use of chemicals or antibiotics, 2) healthier, 3) tastier and 4) public health concerns (including the environment).

Skeptics maintain that organic food is no healthier or tastier than non-organic* foods, and that the possible effects on public health and the environment do not warrant the increased price.² Indeed, under heavy industry pressure, the USDA takes no official position as to whether organic food offers any benefits to human or environmental health.

This paper reviews some of the available data regarding both the personal and public health risks and benefits of organic versus non-organic foods. Three main topics will be covered. The first topic concerns whether there is any evidence that organically produced food offers increased nutritional value. Of specific interest is the growing body of evidence that organic food contains higher levels of flavonoids, and the health implications of increased flavonoid consumption.

The second topic is the effect pesticides have on both consumers of non-organically produced food, and on laborers who are continually exposed to relatively high levels of synthetic pesticides. Recent studies have suggested a link between occupational exposure to pesticides and increased risk for certain types of cancer.

The third topic is the public health impact of persistent delivery of subtherapeutic levels of antibiotics to food animals. While livestock that will be sold as organically certified meat cannot consume antibiotics, most livestock in the United States are fed large amounts of antibiotics throughout their lives to promote growth. In recent years, we have seen increasing levels of antibiotic-resistant pathogens. More and more studies are strongly suggesting that there is a connection between consumption of antibiotics by livestock and the spread of antibiotic-resistant illnesses in humans.

I. Nutritional Benefits of Organic Food

The rising interest in organic foods have coincided with an expanded awareness of the health effects of what we eat. It is not surprising that investigators are probing the link between organic production methods and the nutritional content of foods. Of particular public interest is a group of nutrients popularly known as “nutraceuticals,” compounds naturally found in food products that have been shown to yield a health benefit in clinical trials. Examples of nutraceuticals include flavonoids, antioxidants, beta carotene, and anthocyanins. Supporters of organic farming argue that pesticides decrease levels of nutraceuticals, thereby giving organic food a health benefit.

Flavonoids are a class of phenols which occur naturally in fruits and vegetables. Recent studies have shown that flavonoids offer cardiovascular benefits and possible diminished risk for cancer, although the mechanism of action is unclear. This section reviews the limited data on the differing flavonoid concentration in organic versus non-organically grown produce, as well as the most recent literature regarding the health benefits of flavonoids.

* The term used in popular media and in scientific literature for foods produced without organic methods is “conventionally produced” food. However, organic production was the sole method of production during over 99% of the several millennia in which humans have engaged in agriculture, and even today is far from a marginal production system. Therefore, the term “conventional” seems inapt to describe a relatively young production regime. The term “non-organic” will be used here.

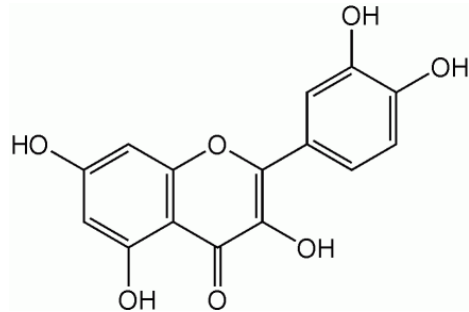


Figure 1. Molecular structure of quercetin (a flavonoid)

A. Flavonoid Content of Organic and Non-Organic Foods

Earlier this year, a study done by Mitchell, et al., set out to compare flavonol[†] content in organically versus non-organically grown tomatoes. The most common source of error in such studies is the inability to control for all the factors contributing to the nutritional content of food (e.g. soil quality, climate, etc.). In this study, however, flavonol levels were measured from dried tomato samples that had been archived for ten years from a plot of land that was concurrently being used in a separate study testing the efficacy of 10 different cropping systems.³ Because of this unique setup, many factors were already being controlled for, such as irrigation, crop rotations and climate, thereby allowing more accurate analysis of the soil fertility management practices. Non-organic plots received pesticides and insecticides as needed, as well as nitrogen containing fertilizers, whereas organic plots received no synthetic chemicals.

Results showed that organically grown tomatoes had higher levels of quercetin and kaempferol ($P < 0.05$) (see Figure 2), and the difference was statically significant. Not only was this difference persistent across the ten year period, but the gap between flavonol content of organically versus non-organically grown tomatoes increased across time.[‡] The authors attributed this difference to the amount of nitrogen available to the plants (see Figure 2). Because organic plants do not grow in fertilizer but rather in manure, the nitrogen levels are significantly lower. As presented in previous studies on plant defenses, lower levels of ambient nitrogen induce a transcription factor which upregulates the production of flavonols.⁵ Flavonols have been found to be helpful in plant health by inducing nitrogen fixing bacteria and repelling harmful insects while attracting other insects important for cross pollination. Another theory explaining the increased flavonol content is that plants increase antioxidant production in response to biotic and abiotic stresses. Therefore, plants which are exposed to pesticides do not upregulate antioxidant production, which results in lower flavonol content of non-organically grown produce.⁶ Similar results have been found in studies of flavonoid content of red oranges⁷ and apples⁸.

[†] Flavonols are a subcategory of flavonoids. Quercetin and kaempferol, discussed *infra*, are members of the flavonol family.

[‡] The authors propose that some of the increase over time was due to deterioration of flavonols of earlier samples in storage. However, as this phenomenon would affect both groups of tomatoes equally, there was still a significant difference of flavonoid content between organic and non-organically grown tomatoes.

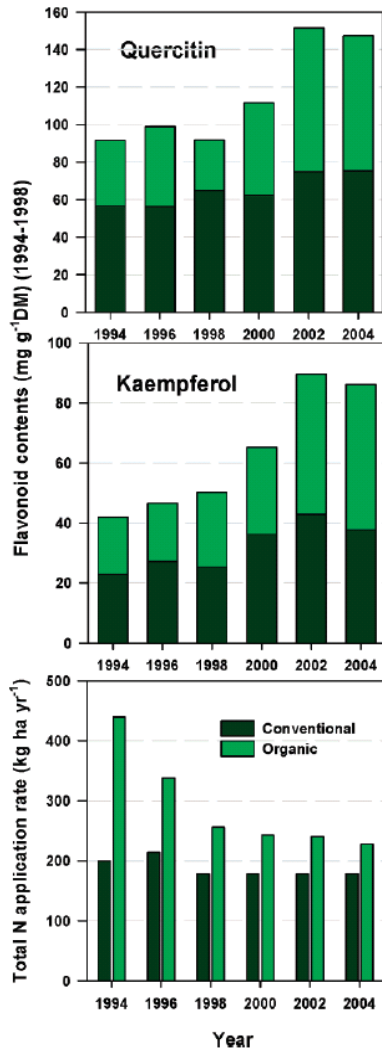


Figure 2. Changes in flavonoid levels over 10 yrs and changes in N inputs over 1994-2000

the study did not examine all flavonols present in apples; therefore, it is possible that the stroke protective properties of apples were due to a class of flavonols other than quercetin. Also, the estimation of quercetin content in foods was based on data from another country. As will be discussed later, content of flavonoids can vary greatly depending on climate and farming technique.

B. Flavonoids and Health

Studies investigating flavonoid content of organic versus non-organically grown fruits are nearly uniform in their conclusion that flavonoid levels in organic food are higher. However the significance of increased flavonoid content on human health is still in dispute.

A study done by Knekt, et al., in 2000, examined the relationship between intake of the flavonoid quercetin and the subsequent incidence of cerebrovascular disease (CVA). A cohort of 9208 Finnish men and women aged over 15 years and without preexisting cardiovascular disease were prospectively followed for 28 years (1967-1994), and CVA incidence was assessed. During this time period, subjects underwent annual interviews regarding their diet from the previous year. Intake of flavonols was estimated using food composition values from a previous analysis done in the Netherlands. Incidence of CVA during follow-up was obtained from data from the Finnish Hospital Discharge Register.

The results showed an inverse association between intake of apples, a food high in flavonoids, and embolic or thrombotic stroke. The relative risk was 0.59 (CI= 0.35-0.99; P=0.45) for men and 0.61 (CI= 0.33-1.12, P=0.02) for women. For quercetin alone, however, the relative risk was 0.95 (CI= 0.6-1.5, P= 0.78) for men and 0.79 (CI 0.48-1.29, P= 0.92) for women, thereby not supporting the hypothesis that quercetin alone was the responsible agent for the decreased incidence of strokes in this study (see Table 1).⁹ The authors do note, however, that the

Table 1 Relative risk^a of cerebrovascular disease between the highest and lowest quartiles^b of quercetin, apple and onion intake

Cerebrovascular disease (ICD-8 code)	Sex	Number of cases	Dietary variable								
			Quercetin ^c			Apple			Onion		
			Relative risk	95% confidence interval	P for trend	Relative risk	95% confidence interval	P for trend	Relative risk	95% confidence interval	P for trend
All (430-438)	Male	445	0.99	(0.71-1.38)	0.80	0.65	(0.45-0.94)	0.85	0.83	(0.61-1.14)	0.42
	Female	378 ^d	0.85	(0.60-1.21)	0.62	0.95	(0.60-1.51)	0.29	1.01	(0.71-1.42)	0.14
Acute strokes (430-434)	Male	309	0.95	(0.65-1.41)	0.60	0.70	(0.45-1.07)	0.56	0.87	(0.60-1.25)	0.79
	Female	259 ^d	0.73	(0.48-1.12)	0.65	0.77	(0.44-1.33)	0.18	1.37	(0.91-2.08)	0.01
Thrombosis or embolia (432-434)	Male	236	0.95	(0.60-1.50)	0.78	0.59	(0.35-0.99)	0.45	1.11	(0.72-1.71)	0.68
	Female	197 ^d	0.79	(0.48-1.29)	0.92	0.61	(0.33-1.12)	0.02	1.44	(0.90-2.31)	0.008
Intracerebral haemorrhage (431)	Male	55	1.09	(0.45-2.62)	0.65	0.84	(0.32-2.19)	0.41	0.60	(0.26-1.37)	0.35
	Female	40	0.53	(0.18-1.55)	0.74	0.61	(0.15-2.49)	0.49	1.12	(0.38-3.30)	0.84

A more recent study on flavonols was done by Edwards, et al., looking at the association between quercetin and hypertension. A group of 41 hypertensive and prehypertensive men and women were enrolled in a double-blind, placebo controlled, crossover study examining the efficacy of consuming 730 mg of quercetin per day versus placebo in lowering blood pressure over 28 days.

The results did not show significant improvement in prehypertensive patients, but did show an added benefit for hypertensive patients. Reductions in systolic blood pressure of -7 ± 2 mmHg ($P < 0.01$) and diastolic blood pressure of -5 ± 2 mmHg ($P < 0.01$) and mean arterial pressures of -5 ± 2 mmHg ($P < 0.01$) were observed in stage 1 hypertensive patients after treatment.¹⁰ The average daily intake of quercetin is 80-480 mg/day, significantly lower than the amount used in the study.⁸

Besides heart disease, flavonoids have also been promoted as a cancer preventing agent. In 2007, Nishikawa, et al., published a multiethnic prospective cohort study involving 183,518 subjects from Hawaii and California. They gathered diet data for four years (1993-1996), but continued to follow them for an additional eight years to assess incidence of pancreatic cancer. Diet was assessed using a quantitative food questionnaire.

In the eight years of follow-up, 529 cases of exocrine pancreatic cancer were reported. Their results showed that intake of total flavonols was associated with a reduced risk of pancreatic cancer (relative risk 0.77, 95% confidence interval; 0.58, 1.03, $p = 0.046$). Of the three flavonols measured, kaempferol was associated with the largest risk reduction, but all flavonols were associated with significant inverse trend among current smokers.¹¹ As smoking is one of the few known risk factors for this fatal type of cancer, the significance of increased flavonol intake and its effect on incidence of pancreatic cancer is particularly important for this high risk population.

Conclusions

Repeated studies show that organic vegetables have higher levels of nutraceuticals such as flavonols when compared to non-organically grown produce. However, with the exception of the study on tomatoes done by Mitchell, et al., most studies comparing nutrient content do not exert sufficient control on the numerous variables involved in farming. This makes it difficult to attribute all differences in nutrient content to farming technique alone. Recent studies support an association between flavonol ingestion and benefits with respect to chronic health conditions such as hypertension, pancreatic cancer, and heart disease. Future studies should focus on the mechanism of nutraceuticals to explain these associations.

⁸ Interestingly, the group also measured indices of oxidant stress in plasma and urine in an attempt to establish a mechanism behind the effect of quercetin. No significant differences were appreciated between the quercetin group versus placebo.

II. Pesticides

According to the EPA, a pesticide is any substance or mixture of substances intended for preventing, destroying, repelling or mitigating any pest. This term applies to herbicides, fungicides and certain other substances used for pest control.¹² Non-organic farming techniques rely heavily on pesticides to increase productivity and minimize losses. Because of the volume of pesticides used in fruit and vegetable production, there has been increasing concern about the health effects of consumption of and exposure to pesticides.

<u>Ten Fruits and Vegetables with the Highest Pesticide Loads</u>	<u>Ten Fruits and Vegetables with the Lowest Pesticide Loads</u>
Peaches	Onions
Apples	Avocado
Sweet Bell Peppers	Sweet Corn – Frozen
Celery	Pineapples
Nectarines	Mango
Strawberries	Sweet Peas – Frozen
Cherries	Asparagus
Lettuce	Kiwi
Grapes – Imported	Bananas
Pears	Cabbage

Table 2. Fruits and vegetables with highest and lowest pesticide residue

A. Ingestion of Pesticides

Very few studies have documented the effects of ingesting pesticides in relatively low levels** on human health. However, in one study, Juhler, et al., investigated the semen quality of farmers who followed an organic versus non-organic diet. Food frequency data and semen were collected from 256 farmers (171 traditional farmers and 85 organic farmers). Each farmer delivered one semen sample. The farmers were divided into three groups of organic food consumption: no (N, 0%), medium (M, 1-49%), or high (H, 50-100%). The current individual dietary intake of 40 pesticides was estimated using food frequencies and generalized serving size data in combination with data on pesticide concentrations in food commodities. The estimated pesticide intake was significantly lower among farmers of group H, but for all three groups of farmers the average dietary intake of 40 pesticides was at or below 1% of the acceptable daily intake (ADI) established by the E.P.A., except for the dithiocarbamates (max = 0.21 microg/kg day = 2.2% ADI), methidathion, (max = 0.01 microg/kg day = 1.4% ADI), and 2-phenylphenol (max = 0.21 microg/kg day = 1.1% ADI).

The median sperm concentration for the three groups of farmers was not significantly different ($p = 0.40$, median sperm concentration was N = 62, M = 44, and H = 75

** The U.S. Environmental Protection Agency regulates the levels of pesticide residue that may be present in foods sold in the United States. The E.P.A. establishes the Acceptable Daily Intake (ADI) of pesticides, discussed *infra*.

million/ml). However, the group of men with no organic food intake had a significantly lower proportion of morphologically normal spermatozoa. Because the only statistically significant difference between the groups was the sperm morphology, the study concluded that the 40 pesticides studied did not heighten the risk of impaired semen quality. The authors acknowledged, however, that studies examining different pesticides or populations exposed to increased levels may see different results.¹⁴

Table 2. Sperm parameters and sex hormones among Danish farmers in relation to percentage intake of organically grown fruit and vegetables (level of significance is indicated by the p value)

	Group N Organic Intake 0% n = 166	Group M Organic Intake 1–49% n = 39	Group H Organic Intake 50–100% n = 46	p Value ^a
Volume (ml) ^b Median (25–75 perc)	3.4 (2.4–5.1)	3 (2.5–4.3)	3 (2.3–3.6)	
Concentration, mill/ml				
Median (25–75 perc)	62 (35–104)	44 (27–89)	75 (32–125)	0.40 ^c
Total count, ^b mill.				
Median (25–75 perc.)	221 (129–405)	169 (78–281)	239 (73–371)	0.77 ^c
Percentage nonvital spermatozoa				
Median (25–75 percentile)	31 (23–42)	32 (23–57)	28 (21–35)	0.32 ^c
Percentage normal sperm heads (WHO)				
Median (25–75 percentile)	39.5 (33–45.5)	41.8 (36.5–49)	41.5 (35.5–46.5)	0.06 ^c
Percentage with tail, midpiece or cytoplasmic defects				
(WHO) Median (25–75 percentile)	13 (10–18.5)	13.5 (8–16.5)	14 (10–19)	0.59 ^c
Percentage normal spermatozoa (strict criteria)				
Median (25–75 percentile)	2.5 (1–4.3)	3 (1.5–4.3)	3.7 (2.5–6.3)	0.003 ^c

B. Occupational Exposure to Pesticides

Farm workers are exposed to levels of pesticides much higher than the average consumer. For this reason, they have become a well-studied group with regard to the effects of pesticide exposure.

A study done by Mills, et al., looked at the incidence of gastric cancer between 1998 and 2003 among California farm workers. One hundred new cases were identified during this time period. Subjects were compared to 210 control participants matched by age, gender and ethnicity. The authors found that work in the citrus industry was associated with increased risk of gastric cancer (OR= 2.88; 95% CI= 1.02-8.12). Specifically, they found that working in areas high in phenoxyacetic acid herbicide (OR= 1.85), organochlorine insecticide chlordane (OR= 2.96), or acaricide propargite and triflurin (OR= 2.86) were associated with increased risk of gastric cancer. They suspected the mechanism was increased ingestion of the aerosolized pesticides causing irritation of the gastric mucosa, allowing direct contact with the cells.¹⁵

These findings are certainly of concern to the citrus workers in California, but they may also pose a greater public health risk. Detectable levels of the pesticides included in this analysis have been found in the ambient atmosphere of the San Joaquin Valley.

A similar study was done in France to assess the incidence and etiology of brain tumors in those exposed occupationally to pesticides. A non-statistically significant increase in risk was found for brain tumors when all levels of occupational exposure to pesticides

were considered (OR = 1.29, 95% CI 0.87 to 1.91). However, in the highest quartile of exposure, a significant association was found for brain tumors (OR = 2.16, 95% CI 1.10 to 4.23) and for gliomas (OR = 3.21, 95% CI 1.13 to 9.11), but not for meningiomas.^{††} The authors concluded that occupational exposure increases the risk of brain tumors, especially gliomas.¹⁶

Conclusions

There is limited data regarding the health implications of ingestion of pesticide residues, perhaps because pesticide residue loads in food are tightly regulated by the E.P.A. However, the data regarding occupational exposure to pesticides is overwhelming. Numerous studies have shown associations with gestational diabetes¹⁷, Parkinson's disease¹⁸, farmer's lung¹⁹ and various cancers.^{20, 21, 22} Even without evidence that personal consumption of pesticides impacts long term health, it would be socially responsible to minimize or eliminate pesticide use for the safety of agricultural workers. Significant resources should be directed to developing pesticide-free farming techniques such as integrated pest management (IPM).

III. Public Health Concerns: Antibiotic Resistance

In the United States, foodborne illnesses have been estimated to cause approximately 76 million illnesses, 325,000 hospitalizations and 5000 deaths each year.²³ The pathogens of greatest concern today are *Campylobacter jejuni*, *E. coli* O157:H7, and *Salmonella* (see Figure 3). Traditionally, the main source of these infections was infected meat products. While this is still true, there are two new trends in foodborne illness that are of concern from a public health perspective. The first is the increasing incidence of multidrug resistant foodborne illnesses from both meats and vegetables. The second is an increase in community-acquired antibiotic resistant illnesses.

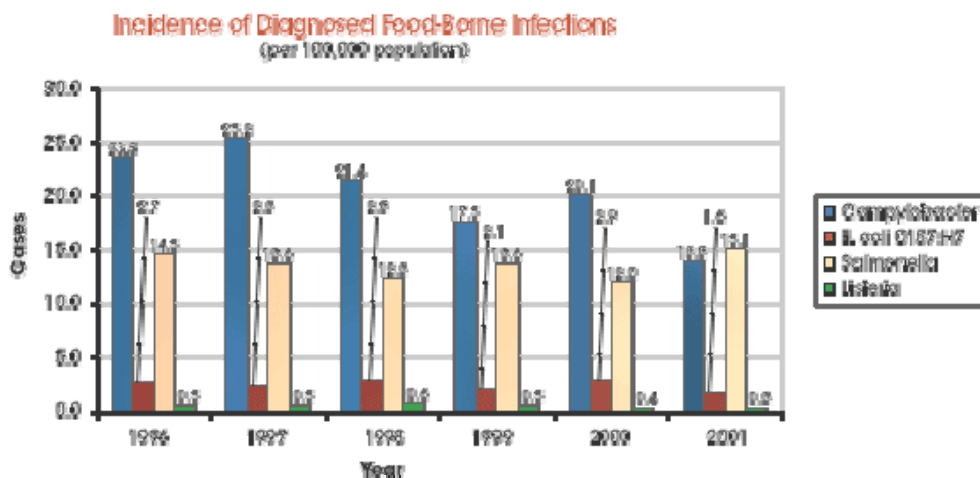


Figure 3. Incidence of foodborne infections from 1996-2001 in United States

Many recent studies have implicated the increasing use of antibiotics for growth promotion in livestock as one of the main causes of the increase in both foodborne

^{††} Perhaps surprisingly, a significant increase in risk was also seen in people who treated their house plants with pesticides (OR = 2.24, 95% CI 1.16 to 4.30).

antibiotic-resistant illness and community-acquired antibiotic-resistant illness. Antimicrobial growth promoters (AGP) are commonly added to the feed of food animals to enhance their growth rate and production performance. The mechanism by which AGPs work is unclear, although different theories exist. It is known that AGPs reduce the normal intestinal flora of animals; it has been proposed that this decreases nutrient competition in the gut, allowing for increased absorption by the animal. AGPs also kill harmful gut bacteria that may reduce performance through subclinical disease.²⁴ It has been shown that animals that receive antibiotics in their feed gain 4-5% more body weight than those who do not.²⁵

The amount of antibiotics dedicated to animal feed is staggering. In Denmark in 1994, 24kg of vancomycin was used for human therapy whereas 24,000 kg of avoparcin (another glycopeptide) was used in animal feed. In Australia, an average of 582 kg of vancomycin was imported per year between 1992-1996 for human use. Approximately 62,000 kg per year were imported during that same time period for use in animal husbandry.²⁶

A. Multidrug Resistant Foodborne Illness from Animal Products

In 2001, White, et al., conducted a study to assess the prevalence of Salmonella in ground meats from retail stores in Washington, D.C. Two hundred samples of ground meat from various animal farms were sampled from three different stores and tested for the presence of Salmonella as well as antibiotic sensitivity panels. The results showed that 20% of all samples contained one of thirteen serotypes of Salmonella. Even more disconcerting was

Table 4. RESISTANCE PHENOTYPES OF SALMONELLA ISOLATED FROM GROUND MEAT.

ANTIMICROBIAL AGENT	MIC*	GROUND CHICKEN	GROUND TURKEY	GROUND PORK	GROUND BEEF	TOTAL (N= 45)
		(N= 20)	(N= 12)	(N= 10)	(N= 3)	
	µg/ml	no. of resistant strains (%)				
Phenicol						
Florfenicol†	≥ 8	3	0	4	0	7 (16)
Chloramphenicol	≥ 32	3	0	4	0	7 (16)
Penicillins						
Ampicillin	≥ 32	3	4	4	1	12 (27)
Amoxicillin-clavulanate	≥ 32	2	4	0	1	7 (16)
Cephalosporins						
Cephalothin	≥ 32	2	4	0	1	7 (16)
Ceftiofur†	≥ 8	2	4	0	1	7 (16)
Ceftriaxone	≥ 64	2	4	0	1	7 (16)
Tetracycline	≥ 16	20	7	8	1	36 (80)
Aminoglycosides						
Amikacin	≥ 64	0	0	0	0	0
Apramycin†	≥ 32	0	0	0	0	0
Gentamicin	≥ 16	2	0	0	0	2 (4)
Kanamycin	≥ 64	2	0	1	0	3 (7)
Streptomycin	≥ 64	19	7	6	1	33 (73)
Sulfonamides and potentiated sulfonamides						
Sulfamethoxazole	≥ 512	11	6	9	1	27 (60)
Trimethoprim-sulfamethoxazole	≥ 4	1	4	2	1	8 (18)
Quinolones and fluoroquinolones						
Nalidixic acid	≥ 32	0	0	0	0	0
Ciprofloxacin	≥ 4	0	0	0	0	0

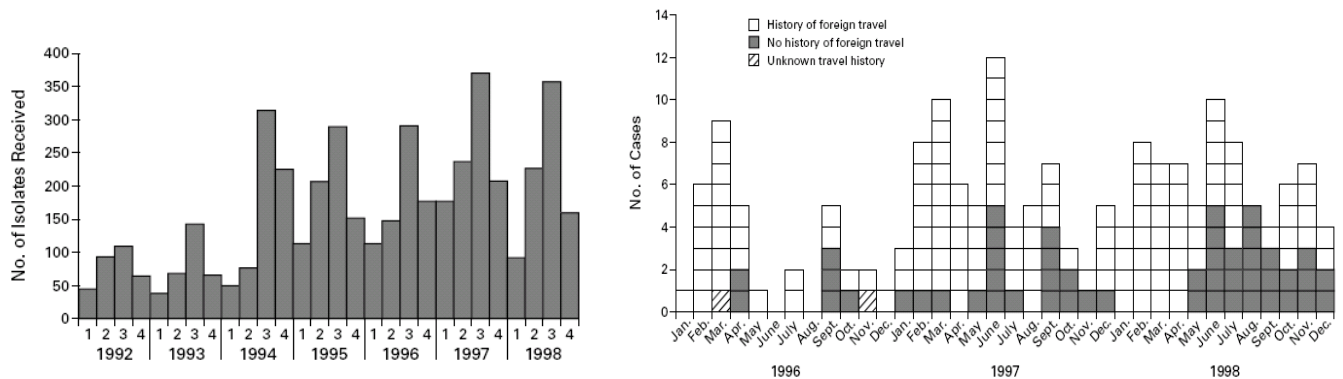
that 84% of the isolates were resistant to at least one antibiotic, and 53% to at least three antibiotics. Five of the isolates showed resistance to 9 of the antibiotics tested and two of them were resistant to 12 of the 17 antibiotics tested (see Table 4).²⁷

Critics argue that most of the resistance was in tetracycline, streptomycin and sulfamethoxazole. Except for the sulfa drugs, these classes of drugs are not commonly used in humans. In adults, the quinolones are the drug of choice for treatment of Salmonella, and there was no resistance to that antibiotic

detected in this study.

However, in a study done in 1999 by Smith, et al., increasing resistance to quinolones among *Campylobacter* isolates was detected. This longitudinal study was conducted in Minnesota from 1992-1998. During that time period, the Minnesota Department of Health received 4953 isolates of *Campylobacter* from humans. The number of domestically acquired *Campylobacter* infections increased from 0.8% in 1996 to 3% in 1998 ($P=0.002$) (see Figure 4).^{‡‡} The authors could only attribute a maximum of 15% of this increase to prior use of quinolones by the patient. The authors recorded that six of the seven subtypes of quinolone resistant *C. jejuni* isolated from chicken products were identical to the subtypes found in humans with domestically acquired *C. jejuni* infections. Notably, the increasing resistance patterns from the time period of 1996-1998 happens to parallel the approval of two other fluoroquinolones (sarafloxacin and enrofloxacin) for use in poultry in the United States.²⁸ This pattern of increasing quinolone resistance in humans after introduction of quinolones in livestock had previously been documented in Europe and Taiwan.²⁹ Because of multiple studies showing similar results, the F.D.A. banned the off-label use of fluoroquinolones in animals used for food but has not banned use of the drugs entirely.

Figure 4. Incidence of *C. jejuni* in (left) all comers and (right) domestically acquired



B. Foodborne Illness from Plants

The etiology of foodborne illnesses from animals and animal products is simple to understand. Consumption of infected meat causes infection. In recent years, however, there have been increasing reports of foodborne illnesses from plants such as lettuce and spinach. Investigators have concluded that these outbreaks have been caused by runoff from nearby animal husbandry facilities, and the use of animal manure as a growing medium. For reasons discussed above, the persistent use of antibiotics in animal husbandry therefore raises the specter of antibiotic-resistant illness from fruits and vegetables, many of which are traditionally consumed raw.

^{‡‡} It should be noted that, during the period from 1992 to 1998, the proportion of quinolone resistant *C. jejuni* increased from 1.3% in 1992 to 10.2% in 1998 ($P<0.001$). Much of this increasing resistance was accounted for by foreign travel and recent use of a quinolone prior to submission of the stool sample. This illustrates the point that, while antibiotic use in livestock seems to increase antibiotic resistance, it is far from the only cause.

In 1996, a multistate outbreak of *E coli* O157:H7 was recorded in both Connecticut and Illinois. Pulsed field gel electrophoresis (PFGE) helped both states trace the *E coli* back to a single grower-processor. Multiple high risk practices were identified at that farm, including no hand washing facilities for staff outside of the portable toilet, no gloves being used during lettuce processing, and the use of unchlorinated water for rinsing. However, the main cause of the outbreak was thought to be water contamination with cow manure from runoff from a nearby beef cattle pasture. The outbreak resulted in illness in at least 61 people, 21 hospitalizations and 3 cases of hemolytic-uremic syndrome.²⁹

In 2000, there was another national outbreak of foodborne illness from lettuce, but this time the pathogen was multidrug resistant *Salmonella* in England and Wales. Between August 1st and September 15 of that year, 361 cases of *Salmonella enterica*, phage type DT104 were isolated. This particular strain is known to be resistant to ampicillin, chloramphenicol, streptomycin, sulphonamides, spectinomycin and tetracyclines. In previous literature, this strain of *Salmonella* had been widely recognized in food producing animals.³¹ Unlike the *E coli* outbreak, the contaminated lettuce was traced back to approximately three separate farms. The suspected mechanism behind the outbreak was multifactorial, related to water contamination from pesticides (runoff), or use of human or animal sewage as crop fertilizer.³⁰ These cases highlight the fact that multidrug resistant foodborne illness is no longer limited to animals and animal products anymore.

As mentioned previously, the transmission of foodborne illness to humans from meat is a straightforward mechanism. In contrast, there have been multiple theories regarding how infection is transmitted to plants and then to humans. Some propose that the manure is improperly treated prior to being applied as fertilizer.² Others support contaminated surface runoff from cattle as a possible source, as was the case in the two epidemics described above. In both cases, investigators have historically assumed that fecal contamination is limited to the surface of the vegetables, and that consumers have not sufficiently washed the products prior to consumption.³⁰

An interesting study done in 2002 by Solomon, et al., however, implies that contamination may be internal to the plant, a mechanism that would be much more difficult to resolve. They investigated whether *E coli* O157:H7 associated with contaminated manure or irrigation water can be transported from the root system into the edible portion of the lettuce leaf. Fresh cow manure was inoculated with a suspension of *E coli* O157:H7. It was then mixed with soil to give the mixture concentrations of *E coli* ranging from 10^8 to $10^{4\text{§§}}$ colony forming units per gram. Seedlings were planted in the various mixtures. Seedlings were cut approximately one cm above the soil surface to prevent surface contamination. All seedlings were surface disinfected by being dipped in 80% ethanol for 5 seconds and then 0.1% HgCl₂ for 5 or 10 minutes. They were washed twice with sterile water and allowed to air dry. The plates were then illuminated with UV

^{§§} While the inoculation doses are far higher than are normally expected in an agricultural field, this was done merely to be able to detect the *E coli* by photomicrography.

light, allowing the *E. coli* colonies to be detected. Fluorescence microscopy was used to allow laser scanning of the colonies of bacteria.³²

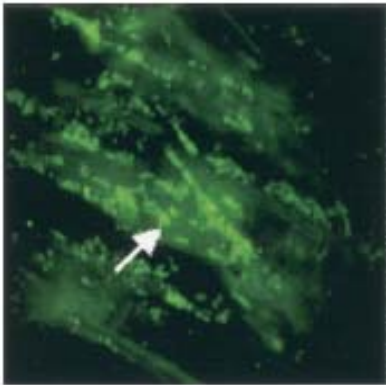
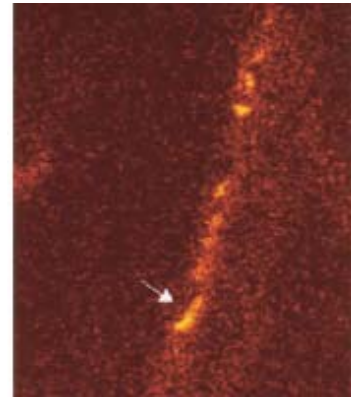


Figure 5.
(left) Photomicrograph showing colonization of lettuce surface with *E. coli* O157:H7
(right) Laser photomicrograph of lettuce showing cells of *E. coli* at 45:μm from outer surface



The study proved that lettuce can, and does, incorporate *E. coli* from the soil into its interior. This is particularly problematic, given that the infective dose of *E. coli* O157:H7 is less than 1000 cells.³³ This study helped establish an alternate route of infection and highlights that direct contact is not required for the infection to be passed. Better hygiene and rinsing techniques may not be enough to prevent foodborne illness from plants.

C. Community-Acquired VRE

Persistent treatment of livestock with antibiotics can lead to not only antibiotic-resistant foodborne illnesses, but also antibiotic-resistant community-acquired illnesses. This section demonstrates how the antibiotic regime applied to animals can cause resistance in humans to crucial antibiotics such as vancomycin and quinupristin-dalfopristin.

Enterococcus is normally found in the gut of all mammals, but it has the ability to cause a wide range of infections, especially in the critically ill. Unfortunately, increasing use of antibiotics for other infections has caused this family of enterococcus to become resistant to most penicillins and cephalosporins, leaving vancomycin (a glycopeptide) as the only alternative. VRE stands for “Vancomycin-Resistant Enterococcus” which includes both *E. faecium* and *E. faecalis*. The first isolate of VRE was found in France in 1986, only to be found shortly later in the United States in 1989. Since then the prevalence of VRE has been rising, accounting for a significant percentage of nosocomial infections in the United States.³⁴

In Europe, the rate of nosocomial outbreaks of VRE has been modest. The amount of community-acquired VRE, however, has been increasing steadily. A study done by Klare, et al., in Germany showed that VRE could be cultured frequently from pigs, poultry and humans in the community, suggesting growth promoters in food animals as a possible source.³⁵

As further evidence, Aarestrup, et al, compared flocks of poultry that had been exposed to growth promoters versus those that had not. No VRE was found in birds raised without growth promoters, whereas 5 out of the 8 flocks raised with growth promoters

showed evidence of VRE.³⁶ A later study done by the same group looked at pigs and poultry. Of 12 pigs herds using feed with avoparcin, 8 had VRE while of the 10 herds not using avoparcin, only 2 had VRE (p=0.043).³⁷

This phenomenon can be extrapolated to the country level (Table 5).

Country	Avoparcin used	VRE in animal husbandry	Ref.
Belgium	+	+	15
Denmark	+	+	13,14
Finland	+	+	16
France	+	+	17
Germany	+	+	7
Great Britain	+	+	6
The Netherlands	+	+	18
Norway	+	+	19
Sweden	-	-	20
United States	-	-	21,22

Table 5. Presence of VRE in food animals as compared to use of avoparcin in food animals

One of the newer antibiotics marketed in 1999 to treat VRE is quinupristin-dalfopristin, a combination of two streptogramins which work synergistically to fight off infection. While this specific antibiotic is not used for growth promotion in animals, virginiamycin, another streptogramin, has been used in farm animals since 1974. A study done by McDonald, et al., looked at the prevalence of quinupristin-dalfopristin resistance in chickens and humans in Georgia, Maryland, Minnesota and Oregon between July 1998 and June 1999. Samples of chicken were obtained from 26 different stores in the four states and 334 stool samples were obtained from outpatients in the same areas. Quinupristin-dalfopristin resistant *E faecium* was isolated from 237 chicken carcasses and 3 stool samples of humans.³⁸ This study was conducted before quinupristin-dalfopristin had been approved for human use in the United States.

Although some find it reassuring that only 3 human stool samples were positive for the resistant form of the pathogen, it is disconcerting that any humans demonstrated resistance to an antibiotic that had not been exposed to the human or animal population at all. The data strongly suggest that resistance developed while the livestock were exposed to a drug in the same class. Consequently, the effectiveness of the new drug was compromised before it was ever approved for human use.

A study done by Hershberger, et al., looked at the prevalence of various antibiotic resistant enterococci from farms in Michigan, Wisconsin and Indiana from 1998 to 2003. They found quinupristin-dalfopristin resistance levels in cattle ranging from 2% in beef cattle to 21% in dairy cattle, 21% in swine, 85% in chicken and 24% in turkey (see Table 6). The higher levels of resistance in the poultry farms correlated with use of virginiamycin in the poultry feed.^{***39}

*** Interestingly, no isolates of VRE were detected. Avoparcin, a drug in the glycopeptide family with Vancomycin, is not used in animal husbandry in the United States.

Farm	<i>E. faecium</i>	
	Q-D-resistant isolates (PFGE groups)	gentamicin-resistant isolates (PFGE groups)
Dairy cattle	51 (28)	42 (12)
Beef	3 (3)	0
Swine	60 (23)	4 (2)
Chicken	62 (50)	9 (9)
Turkey	74 (74)	19 (19)

Q-D, quinupristin/dalfopristin.

Table 6. Resistance to quinipristin-dalfopristin in livestock using virginiamycin

There are many theories regarding the mechanism by which animals colonized with VRE spread the infection to humans. As with foodborne illness, insufficiently heated food and cross contamination are obvious pathways from the animal to the human.

A study done by Sorensen, et al., examined whether ingestion of meats containing resistant enterococcus could lead to detectable levels of VRE in the human gut. They conducted a randomized, double blind study in 18 healthy volunteers. Six volunteers ingested chicken that was positive for glycopeptide resistant *E faecium*, six ingested pig that was positive for streptogramin resistant *E faecium* and 6 ate chicken that had known susceptible strains of enterococcus. Stool samples from the subjects were collected daily for the first week and then at days 14 and 35. Initially, none of the subjects had evidence of VRE in their stool. However, the test strains ingested in their respective groups were isolated from 8 of the 12 subjects on day 6 and from 1 of 12 on day 14. By day 35, stool samples were negative again.⁴⁰ This study shows that ingestion of resistant strains can cause at least transient carriage of resistant bacteria, which may allow enough time for transfer of DNA elements containing antibiotic resistant genes. Evidence of in vivo transfer of streptogramin and glycopeptide resistance has also been documented.⁴¹

A study done by Shoemaker, et al., showed that Bacteroides, another normal colonizer of the human digestive tract, can transfer antimicrobial resistant transposons amongst themselves. It also showed that bacteria that are transiently in the gut or are present in low numbers can share resistance DNA products to the normal colonizers. In this study, it resulted in antibiotic resistance to drugs such as tetracycline and clindamycin in humans who have never been exposed to those antibiotics before.⁴² Combining this data with the study by Sorensen, the greater implication, would be that the repeated transient carriage of VRE or other resistant organisms can cause transfer of resistance patterns to the bacteria colonizing the human gut.

Regardless of mechanism, the evidence was strong enough that in 1998, the food animal industries in Denmark voluntarily decided to stop all use of antimicrobial agents for growth promotion by the end of 1999. In 2001, Aaerstrup, et al., reviewed trends in resistance to glycopeptides, macrolides, and streptogramins from 1995-2000 in Denmark. The group found that, since the ban of AGPs, there was a parallel decrease in resistance patterns in pigs and chickens in animal farms in Denmark(see Figure 6).⁴³ No studies have yet been performed to document a parallel decrease in resistance in humans, but those studies are underway.

In 2006, because of the mounting evidence discussed above, the European Union banned the feeding of all antibiotics and related drugs to livestock for growth promotion

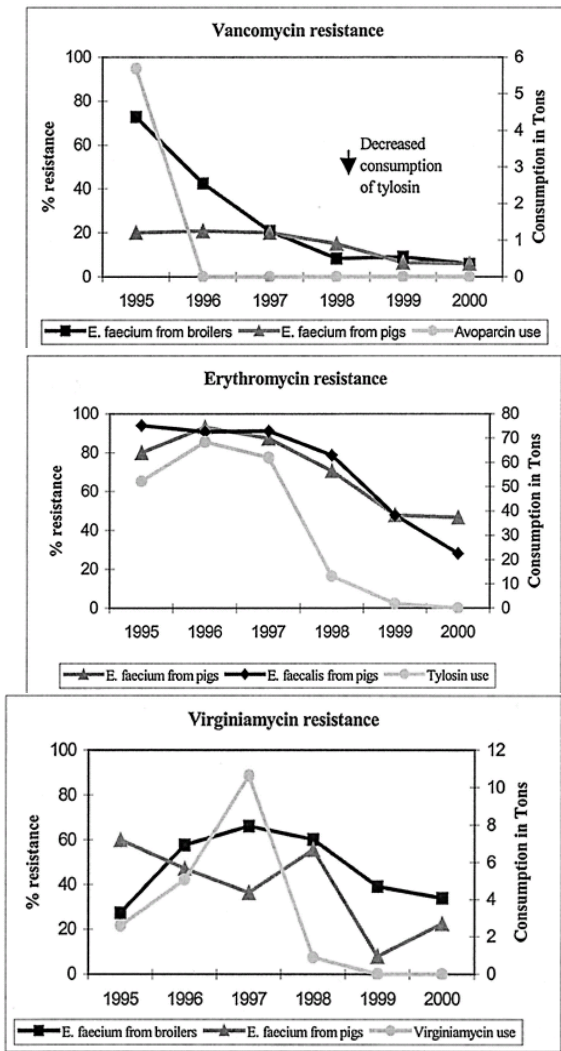


Figure 6. Decreasing resistance to antibiotics following various bans on use of AGPs in Denmark. Avoparcin in 1995, Tylosin in (macrolide) 1998/99 and Virginiamycin in 1998

human use. Europe had previously tried to limit antibiotic use to only those antibiotics not used in human medicine. But with the increasing spread of antibiotic resistance, that class of antibiotics is constantly in flux leading to their complete ban in 2006.

There is no doubt that the primary cause of antibiotic resistance in humans is from antibiotic use in humans. Continued education of proper indications for use of these medications is still important. However, eliminating use of antibiotics in animals will also help reduce the selective pressure that causes multidrug resistance.

purposes. This expanded on their previous 1998 policy, which banned the feeding of antibiotics that are valuable in human medicine to livestock for growth promotion. Now, no antibiotics can be used in European livestock for growth promotion purposes.⁴⁴

Conclusions

There is an increasing public outcry for the limitation of antibiotics used as growth promoters in livestock. As reviewed here, this is based on copious data showing the direct association of AGP use with increasing antibiotic resistance in the human population. While foodborne illness will always be a public health issue, it will be much more difficult to control in the future if the infections are resistant to multiple antibiotics.

The main argument against banning AGPs is decreased production of livestock secondary to increased infections.⁴⁷ These infections, however, are largely due to poor hygiene of the animals kept in small holdings that are close together. While organic farms do currently report lower productivity than non-organic farms, the difference has been decreasing as newer organic techniques have been implemented.

The rate of production of truly new antibiotics has declined in the last 20 years, causing us to turn to medications we had not previously considered for

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