

Pesticide

between breast cancer, exposure to common chemicals

The most striking study to date, published in April by Mary Wolff of Manhattan's Mount Sinai Medical Center, found that women whose blood contained high concentrations of residues from the banned pesticide DDT — a known estrogenic chemical — were four times as likely to get breast cancer as women with low concentrations in their blood. Breast cancer risk rose steadily as the level of DDT residue increased, Wolff found.

A cascade of research linking estrogenic chemicals and breast cancer — including the insecticide beta-HCH and the electrical insulators known as PCBs — has captured the attention of the nation's cancer research establishment, which has traditionally spurned environmental studies and focused instead on treatment techniques and genetics.

When it published the Wolff study, the Journal of the National Cancer Institute editorialized that the research "may have extraordinary global implications for the prevention of breast cancer" and should serve "as a wakeup call for urgent research."

"The environmental hypothesis is extremely interesting and scientifically important, and we're going to pursue it," said Dr. Samuel Broder, director of the National Cancer Institute. "This is an area that is certainly high priority, and it's very important to me personally."

Broder said he has a special reason to be interested: his wife has breast cancer, and her sister died of the disease; both grew up in a Bellmore neighborhood where breast cancer seemed un-

usually common, he said.

"It's a high priority for us, and particularly for NCI," agreed his boss, Secretary of Health and Human Services Donna Shalala. "We're going to aggressively pursue and put resources into breast cancer, and we're going to focus on prevention."

Many scientists remain skeptical.

They emphasize that there is no one cause of the disease, and suggest that genes or diet or some as-yet-unidentified factors may be more important than estrogenic chemicals. If pesticides were so significant, they argue, epidemiologists would have proven by now that breast cancer risk is higher in areas where exposures to estrogenic chemicals are high.

"The more I read about the breast cancer issue, the more confused I get," said John McCarthy, chief scientist with the National Agricultural Chemicals Association, the pesticide industry's trade association. "It's clear that the experts are all over the map as to what's causing breast cancer."

While some scientists are already calling for tough restrictions on es-

trogenic chemicals, especially pesticides that are used on food crops, toxicologists at the U.S. Environmental Protection Agency say too little is understood about estrogen-linked cancer to make regulatory decisions. The evidence isn't even strong enough, they say, to justify screening pesticides to determine which mimic natural estrogen.

As a result, few pesticides have been tested to see whether they are estrogenic. Even for the 15 pesticides that have been shown to cause breast cancer in rats the EPA does not require a test for estrogenicity. And not one of those pesticides has been banned by the EPA, even though the agency has banned dozens of pesticides for causing other types of cancer in mice or rats.

"We're still so early in the process of figuring out what's happening in the human population, and understanding the hormonal mechanisms," said Karl Baetcke, an EPA toxicologist who has worked extensively on the breast cancer issue. "I really have no confidence that we're going to make tremendous strides in the next few years in how we deal

with mammary tumors."

Despite the EPA's uncertainty, momentum in the scientific community is shifting as other theories fall by the wayside. Studies have largely discredited the once-popular idea that a high-fat diet increases breast cancer risk. And for all the fierce competition among geneticists seeking to become the first to identify the breast cancer susceptibility gene, that gene is so unusual that it is believed responsible for only one in 20 breast cancer cases.

Earlier this year, the National Cancer Institute announced it was moving ahead with more than a dozen research projects on environmental factors and breast cancer, including a multimillion-dollar effort that will look closely at women on Long Island and elsewhere in the Northeast.

"All of a sudden, everybody is out there now trying to show there are a lot of chemicals in the environment that could cause breast cancer," said Louise Brinton, chief of the environmental studies section at the cancer institute and a breast cancer specialist. Those links are still unproven, she said, but are "provocative and worth pursuing, because there is a plausible biological mechanism behind the association."

Putting the Pieces Together

Like a 1,000-piece jigsaw puzzle that suddenly becomes recognizable when it's almost finished, the toxics-based theory of breast cancer has been constructed from an assortment of seem-

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BREAST CANCER

A SPECIAL REPORT

Third in a series on the disease and its toll on LI

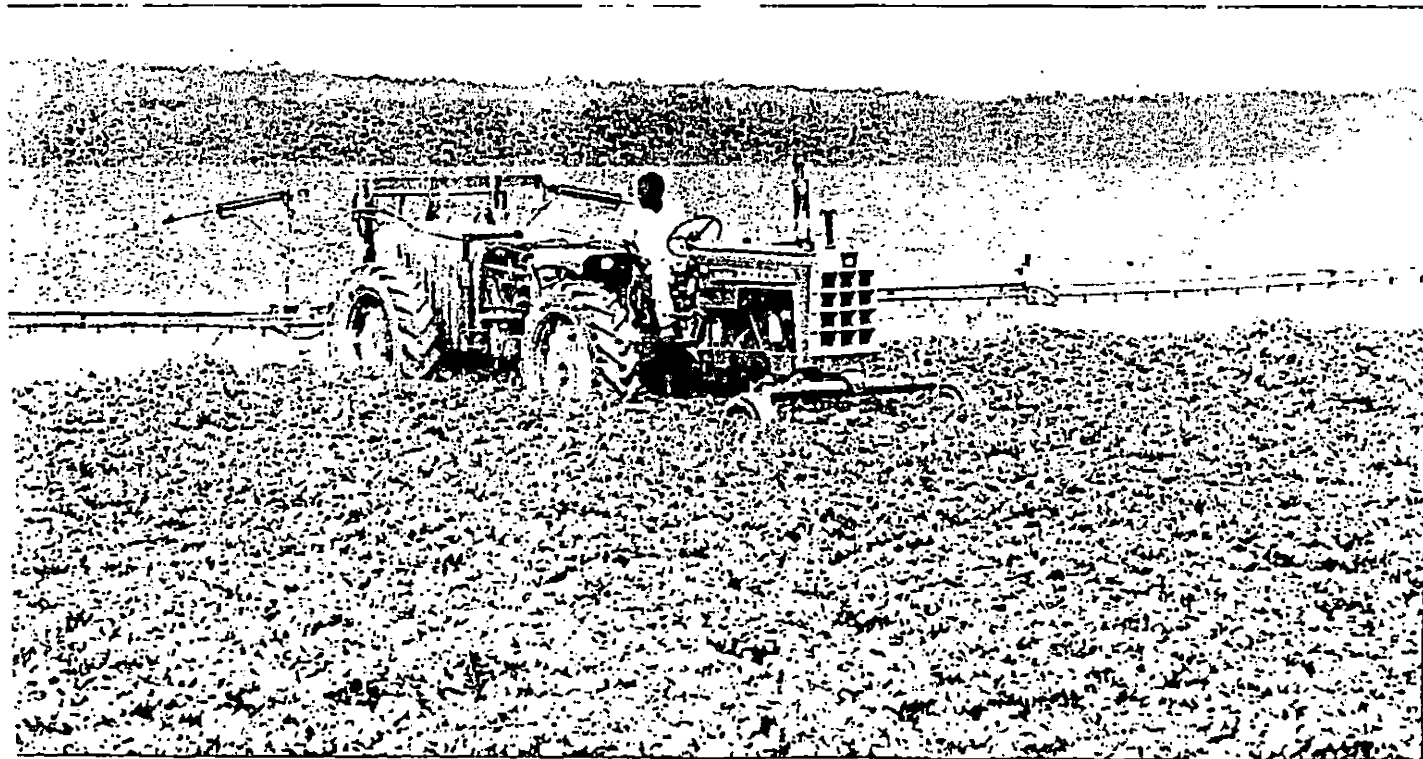
Coming Tuesday:

Examining the possible links between past pesticide use, LI's drinking water and breast cancer

The Series So Far

JUNE 27: Are LIers at greater risk? Study finds an average cancer risk but higher death rate.

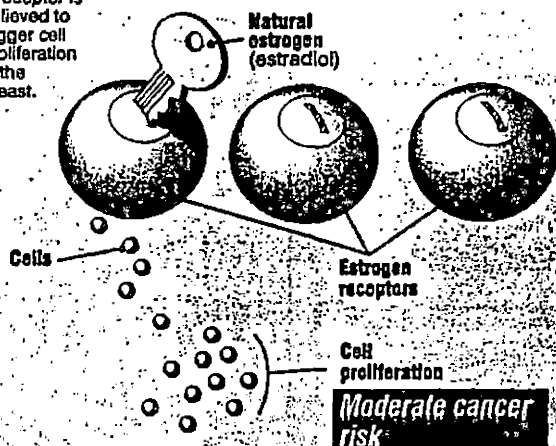
JULY 25: Fran and Jerry Lanzo's Story.



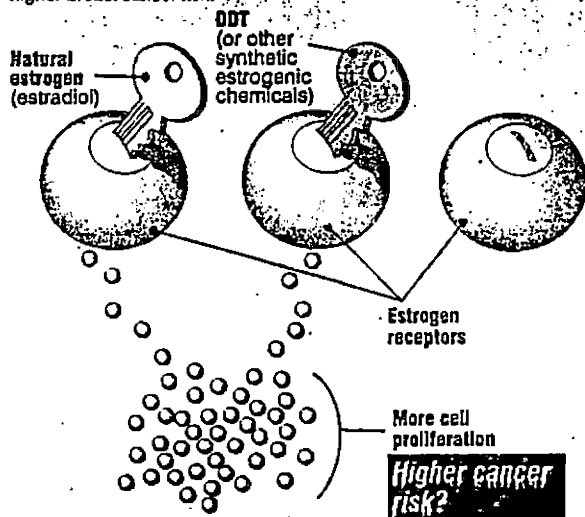
decades on the island's farms, such as this potato field in Bridgehampton shown in 1975, have become key suspects in research probing an increase in breast cancer.

Unlocking Breast Cancer

Scientists used to think that cells known as estrogen receptors function like locks that can only be opened by estradiol, a natural hormone. Higher estradiol levels raise the risk of breast cancer because, when it is "opened," a receptor is believed to trigger cell proliferation in the breast.



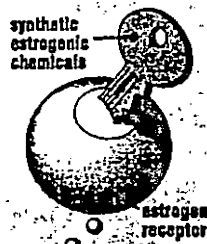
But now researchers have discovered that the "keys" carried by DDT and certain other synthetic chemicals can also open the receptor "locks," suggesting that higher levels of those chemicals in the body may mean higher breast cancer risk.



Suspects

These are among the most well-known compounds that are suspected to bind with estrogen receptor cells. Of this group, DDT and PCBs have been experimentally linked to breast cancer in humans.

- **Chlordane** A termite-killer that was used near foundations of 30 million homes before it was banned in 1983.
- **DDT** The world's leading insecticide until it was banned in the United States in 1972, it is still present in some soils and in the bloodstreams of virtually all Americans.
- **Dioxin** A byproduct of waste incineration, it is also an ingredient in several now-banned pesticides.
- **Heptachlor** A termite-killer, it was banned in 1978.



- **Kepona** Used as bait in ant and cockroach traps until it was banned in 1978.
- **Methoxychlor** An insecticide still used on trees and some vegetables.
- **Nonylphenol** A common ingredient of plastics, industrial detergents, condom lubricants and spermicidal creams.
- **PCBs** (polychlorinated biphenyls): Electrical insulators, they were banned in 1978 but are still found in old transformers and in soil, water, animals and people.

Suspect:

New studies focus on link

First of two parts

By Dan Fagin/STAFF WRITER

Common pesticides are now emerging as key suspects in explaining the dramatic three-decade rise in the incidence of breast cancer.

Increasing evidence suggests that a growing number of chemicals that kill insects, stifle weeds and even lubricate condoms are also able to mimic the effects of estrogen, the group of hormones associated with higher breast cancer risk.

At the same time, new studies are also directly linking some of these chemicals to breast cancer for the first time.

Yet despite growing excitement among scientists about these research discoveries, federal regulators so far have moved slowly—if at all—to catalogue these chemicals or to restrict their use. They say it may be years before they understand estrogen-linked cancers well enough to justify bans or special testing.

As a result, no pesticide has ever been banned for causing breast cancer, even though at least 15 have been shown to cause breast tumors in rats—including the top-selling pesticide in the nation, atrazine. Another 68 industrial chemicals have also been found to cause breast tumors in rats or mice, *Newsday* found in a review of federal records and scientific literature, but human exposure to those chemicals generally is lower than to pesticides.

These are the principal findings of a *Newsday* examination of environmental factors and breast cancer, a baffling potential killer that will strike a record 180,000 American women this year, more than any other kind of cancer.

The disease's origins are largely a mystery. Known risks explain only 30 percent of all cases. But there is an important clue: all of the proven risks except family history are traceable to high lifetime exposure to estrogen, the family of hormones that regulates female sexual development. Women who have their first child late in life for example, or who begin menstruating early, are more likely to get breast cancer.

Now, surprisingly, scientists are discovering that a number of pesticides that have been routinely used in backyards and farm fields also can trigger cell proliferation and biochemical changes that are similar to changes in human cells caused by natural estrogen. And some of those estrogenic chemicals, which can accumulate in human fatty tissue for decades, are now being linked to breast cancer in people and not just rats.

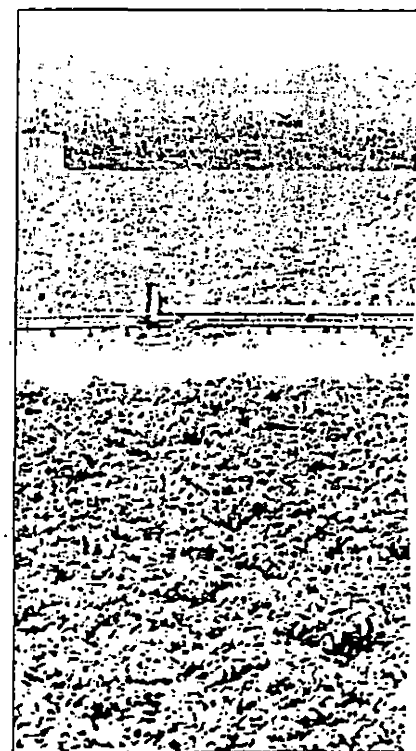
If those studies are confirmed, it would mark the first time that a direct environmental cause has been established for breast cancer, and the focus of the nation's multimillion-dollar battle against breast cancer could shift to prevention, instead of only diagnosis and treatment.

"It seems quite obvious, doesn't it? There's only one common thread tying together all of the known risk factors for breast cancer: the more estrogen exposure in a woman's lifetime, the greater her risk of breast cancer. So why aren't we looking hard at these environmental chemicals that we now know can act like

estrogens? Why aren't we trying to reduce exposures?" said toxicologist Devra Lee Davis. A senior adviser to the U.S. assistant secretary for health, Davis is a key architect of the theory that the synthetic chemicals she calls "xenoestrogens" are a preventable cause of breast cancer.

Even the most ardent advocates don't contend that a woman who is exposed to an estrogenic chemical is somehow fated to develop the disease. But they do assert that more exposure means more risk, and that the proliferation of synthetic chemicals over the past few decades helps explain why the odds that an American woman will get breast cancer by age 85 have skyrocketed, from one in 20 in 1960, to one in eight today.

In its effort to explore this volatile issue, *Newsday* obtained thousands of pages of federal documents under the Freedom of Information Act, interviewed dozens of officials and experts, and reviewed the latest scientific research.



Common pesticides routinely used in past

Studies Probe the Pesticide

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ingly unconnected observations and experiments that have been assembled gradually over the years.

The first clues came from DDT. In "Silent Spring" — published in 1962, a decade before the insecticide was banned — Rachel Carson described how birds (including Long Island ospreys) often couldn't reproduce after being exposed to DDT because of the paper-thin shells of the eggs they laid, a function regulated by estrogen. And by the mid-1970s, evidence was emerging that DDT and PCBs interfere with a mother's ability to produce milk for breast feeding, another estrogen-regulated function.

Meanwhile, breast cancer researchers were noticing that estrogen seemed to figure prominently in most aspects of the disease. They didn't know why — and still aren't sure today — but higher lifetime estrogen exposure seemed to mean higher breast cancer risk.

In the lab, experiments were showing that breast tumors in laboratory rats subsided when the rats' ovaries (the source of natural estrogen) were removed, but returned when the rats were injected with estrogen.

And surveys of women were showing that the ones who were exposed to unusually high levels of estrogen were also more likely to get breast cancer. Having the first child late, menstruating early, entering menopause late, and using early high-dose versions of oral contraceptives and estrogen-replacement therapies all increase lifetime exposure to natural estrogen — and all were being revealed as risk factors for breast cancer.

'It seems quite obvious, doesn't it? . . . So why aren't we looking hard at these environmental chemicals that we now know can act like estrogens? Why aren't we trying to reduce exposures?'

—Devra Davis, U.S. Health Dept. toxicologist



cer. Women whose ovaries were surgically removed, or who entered menopause at an early age, were found to be less likely to get breast cancer.

But there were other curiosities about breast cancer that could not be explained by the body's own estrogen. For one thing, all those known risk factors plus family history could be linked to only about 30 percent of all breast cancer cases. What's more, the disease's incidence began surging in the decades after World War II even though women during those years were having more children than before and were giving birth at an earlier age. And finally, epidemiologists noticed that breast cancer is far rarer among women in Japan, but that the children of Japanese women who immigrate to the United States face the same risk as other American women.

So researchers began to ask themselves: if estrogen is a key to breast cancer, but naturally produced estrogen cannot fully explain the disease's relentless frequency, what can?

Synthetic chemicals were the obvious suspect, because of what happened when chemists created an extremely powerful estrogen called DES, or diethylstilbestrol. The drug was prescribed to millions of pregnant women to prevent miscarriage during the 1950s and 1960s, until researchers realized that daughters of these women were having extraordinarily high rates of vaginal and cervical cancer. DES has not been linked to significantly higher breast cancer risk in humans, but when scientists gave it to rats, the animals almost inevitably developed breast tumors.

DES was a triumph-turned-tragedy of chemical engineering, a compound that had been designed specifically to

trigger the same chemical reactions in the body that are caused by natural estrogen. But, according to the prevailing scientific view, chemicals developed for other purposes couldn't possibly trigger the same estrogenic reactions.

A Surprising Discovery

The prevailing view was wrong. By the mid-1980s researchers had developed ways to screen chemicals to see if they acted like natural estrogen, and began discovering that several synthetic chemicals were estrogenic, including PCBs and the pesticides DDT, beta-HCH, chlordane, Kepone and methoxychlor.

At least one was identified by accident: nonylphenol, a common plastic additive that's also used in condom lubricants, spermicides and industrial detergents. It was discovered when a blood sample was found to be unexpectedly estrogenic, and the problem was eventually traced back to plastic tubing that had tainted the blood.

Of that group, all have been banned except nonylphenol and methoxychlor, which is still sprayed on fruit trees on Long Island and elsewhere. But even those chemicals that have been banned — all for health reasons that have nothing to do with estrogenicity — are still often present in soil, water or in the tissues of people and animals.

So far, fewer than 100 chemicals have been tested for estrogenicity. But some researchers believe scores of common chemicals may eventually be identified as estrogenic because those that have been discovered to date are so diverse.

"It's really quite strange, but there are now [estrogenic] chemicals emerg-

Scientist Who Made the DDT Link

Groundbreaking study stunned researchers



Mary Wolff of Mt. Sinai Medical Center

Mary Wolff doesn't look, act or talk like a revolutionary.

The scientist chooses her words with the same cautious precision that she applies to her work, the measurement of human exposures to toxic chemicals.

But her study linking breast cancer risk to the banned insecticide DDT had a revolutionary effect when it was published in April in the *Journal of the National Cancer Institute*. The study is by far the strongest evidence yet that toxic chemicals may be an important cause of breast cancer, and it has set off a scramble as researchers around the world seek to replicate her findings or find other chemicals that also may increase breast cancer risk.

"The Wolff study is very interesting and provocative. It's generated a lot of new work," said Sheila Zahm, an epidemiologist at the National Cancer Institute. "Within a year or two years there's going to be a lot of new information."

"There's certainly a lot more excitement in this area now that the Wolff study is out," agreed Louise Brinton, chief of the environmental studies section at the cancer institute. "We're all trying to figure out what to do next."

Activist groups like Greenpeace are already using Wolff's research to argue for a broad phase-out of all chlorine-based organic chemicals — a huge family of synthetic compounds that includes many pesticides that are chemically similar to DDT and thus might be linked to breast cancer.

But Wolff refuses to draw such sweeping conclusions based on her work. "Until the data are confirmed time after time it's not going to be considered to be a major causal relationship to breast cancer," she said. "That's just the way epidemiology works."

An associate professor of community medicine at Mount Sinai School of Medicine, Wolff, 50, works in a cramped, windowless office in upper Manhattan, where she does the meticulous work of analyzing blood and tissue samples for minute traces of toxic chemicals.

For the past two years, she has been looking for DDE, a product of the breakdown of DDT. The insecticide has been banned since 1972, but it is so persistent in the environment that DDE residues are present in virtually all Americans, where it accumulates in fatty tissue.

She studied frozen blood samples from 58 New York area women who appeared healthy but would be diagnosed with breast cancer within six months after the blood sample was taken, and compared them with blood from 171 women who were demographically similar to the 58 in every way except that they remained cancer free.

Her conclusion: Women were four times as likely to get breast cancer if they had very high levels of DDE in their blood than if they had very low levels.

The study's biggest drawback is that it was relatively small, and that's why Wolff is now expanding her study by analyzing a larger number of blood samples for DDE.

Once that's finished, she said, she hopes to take part in a much larger environmental study that the cancer institute is preparing to launch of breast cancer risk in the Northeast, including Long Island.

"As I've always said, this may or may not hold up in future studies," Wolff said. "But if nothing else, it will force breast cancer epidemiologists to look at other potential causes. Up to now, there just hasn't been much of that going on."

— Dan Fagin

Connection

ing in the literature almost every month now," said John McLachlan, scientific director of the National Institute of Environmental Health Sciences and a hormone specialist. "Based on what we know now, it wouldn't be surprising if there are a lot of them."

Even though they had begun identifying the suspects, however, scientists still didn't have solid evidence that synthetic estrogens actually cause breast cancer in humans.

The only linkages had been tentative. Two years ago, a Finnish research team found that a pooled blood sample from 44 women with breast cancer had 50 percent more beta-HCH, an estrogenic insecticide, than blood from a control group of cancer-free women. And last year, a Connecticut study found that malignant breast tissue from 20 women contained more than twice as much PCBs and DDT residue as a control group.

Both studies had a serious flaw: Neither was designed to factor out the known risk factors for breast cancer. The women could have gotten cancer not because of exposures to PCBs or DDT, but because the disease ran in their family or because they started menstruating early or had children late. Or, by another theory, the breast tumors could somehow have led to higher blood levels of the toxic chemicals, instead of vice versa.

So when one of the collaborators on the Connecticut study, Wolff of Mount Sinai Medical Center, set out to do another study, she carefully selected her subjects from among almost 15,000 New York-area women who had gotten

mammograms at New York University between 1985 and 1991. Those women had filled out detailed questionnaires and given blood samples, which were then frozen for preservation.

Wolff decided to analyze the frozen blood samples of 58 women who had no sign of breast cancer at the time their blood was drawn, but were diagnosed one to six months afterward. She matched up those 58 women with 171 others who remained cancer-free but were virtually identical to the 58 in age, childbearing history and virtually every other characteristic known to influence breast cancer risk.

What Wolff found startled her.

PCB concentrations were 15 percent higher in the blood of women who would later develop cancer, and DDT residues were 35 percent higher. But what was most surprising is that breast cancer risk rose steadily as the level of DDT residue increased. In fact, the 10 percent of women with the highest amount of DDT residue in their blood were four times as likely to get breast cancer as the 10 percent with the lowest.

That would make DDT one of the most powerful risks for breast cancer ever identified. Stronger than a history of benign breast disease, or a close relative with breast cancer. Stronger than late menopause, early menstruation, or late childbirth. Stronger than being white, or wealthy, or Jewish or living in the suburbs.

"The numbers are terrifying, really. I still can't believe the risk is that

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A Q&A: What Can You Do To Cut Your Risk

By Dan Fagin
STAFF WRITER

The most important thing women can do to reduce their risk of dying from breast cancer is to detect the disease early — through breast self-examination, good medical care and, for women over age 40, yearly regular mammograms.

But when it comes to avoiding breast cancer in the first place, there are frustratingly few things women can do that are proven to cut their risk, because most of the disease's known risk factors are beyond control. Still, experts say there are prudent steps women can take that might reduce their risk, and are worth doing anyway because of other health benefits.

Here's a sampling of the experts' advice:

Question: If I avoid pesticides, will I reduce my risk of getting breast cancer?

Answer: There's no easy answer to that question. There are hundreds of common pesticide formulations on the market, each with unique characteristics and benefits. And there's no proof that any of them cause breast cancer in humans. On the other hand, many are associated with health problems in animals and people. So a general policy of avoiding unnecessary pesticide exposures is advocated by many experts. And when you do use them be sure to strictly follow precautions on the label.

Pesticide exposures should not be considered a reason to avoid eating fruit and vegetables, however. The health benefits of a balanced diet far outweigh any risk that might be associated with pesticide residues. Of course, it's always a good idea to wash vegetables and fruit before eating them.

Q: What about pesticides and other synthetic chemicals that are estrogenic — that mimic the effects of natural estrogen?

A: That depends on whom you ask. The evidence is still inconclusive, but some scientists believe exposure to estrogenic chemicals may be an important risk factor for breast cancer. Few chemicals have been screened for estrogenicity, but many may eventually be shown to be estrogenic because they cause breast cancer or other hormone-related problems in animals.

Q: Should I stop taking birth-control pills, or stop participating in estrogen replacement therapy?

A: Not necessarily. In the early days of the pill and of estrogen replacement therapy, both relied on high doses of estrogen, and both eventually were

associated with increased breast cancer risk. However, current formulations contain far less estrogen, and links to breast cancer are inconclusive at best. The best policy is to discuss both the risks and benefits with your doctor.

Q: Will eating right reduce my risk?

A: Probably. There are many good reasons to stick to a low-fat, high-fiber diet rich in vegetables — and avoiding breast cancer might be one of those reasons. A high-fat diet has not been proven to be a risk factor for breast cancer, but obesity is a proven risk. It's possible that overweight people are at greater risk because some carcinogenic chemicals are attracted to fatty tissue and accumulate there. But that has not been proven.

There's also some evidence that women shouldn't scrimp on vegetables like broccoli, spinach, carrots and sweet potatoes that are rich in beta-carotene, which the body converts to Vitamin A. That's important because Vitamin A is known to have a regulating effect on cell formation, and therefore perhaps on cancer.

The cruciferous family of vegetables — including cabbage, cauliflower, broccoli and brussels sprouts — may be especially beneficial because they contain indole-3-carbinol. The body metabolizes natural estrogen in two ways, but only one of them is associated with higher breast cancer risk. Indole-3-carbinol has been shown to stimulate the safer route of metabolism.

Q: What about drinking alcohol?

A: Even moderate drinking is known to increase the risk of breast cancer, and heavy drinkers face an even higher risk. No one is sure why, but it may be because alcohol recently has been shown to raise estrogen levels in premenopausal women. On the other hand, there is some evidence that having one or two drinks a day — but no more — lowers the risk of cardiovascular disease, which kills more women than breast cancer.

While there are many preventive actions women can take that might reduce their risk of breast cancer, experts emphasize the most important thing is to diagnose the disease as early as possible. The American Cancer Society recommends women 40 to 49 get mammograms every one or two years; and yearly mammograms are essential for women over 50.

An Estrogen Explainer

What It Is. A group of hormones that cause the growth and development of female sexual characteristics in humans and other animals. The body makes three principal forms of estrogen: estrone, estradiol and estril. Estril is the most potent and plentiful.

The increased amount of estrogen in the bloodstream causes development of breasts, maturation of the reproductive tract and the appearance of secondary sexual characteristics. Estrogen regulates the menstrual cycle and stimulates the lining of the uterus to thicken.

At puberty a young woman's ovaries begin to secrete estrogen in response to stimulation from the follicle-stimulating hormone (FSH) produced by the pituitary gland.



Estrogen Levels

A post-puberty and pre-menopausal woman with a normal menstrual cycle secretes about 70 to 500 micrograms of estradiol a day depending on the phase of her menstrual cycle. As a woman grows older her ovaries secrete less estrogen. After menopause estrogen production declines, bones become more fragile and risk of heart attack rises.

Pesticide Peril: Studies Probe

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high," Wolff said.

Wolff's study was relatively small, but its findings were enough to set off a flurry of research as scientists seek to replicate her results, or find similar associations between other synthetic estrogens and breast cancer. The pace quickened in May when another study found that heavy alcohol use, one of the few strong risks that had not been linked to estrogen, did indeed lead to higher estrogen levels in women. And other research has found that women actually face a lower risk of getting breast cancer when they are exposed to the toxic chemical dioxin, which lowers estrogen levels instead of raising them.

"There's a line of research now that is really coming together from very broad fields," said Davis, the toxicologist, who is collaborating on an ongoing study that she said will identify new estrogenic chemicals. "Up to now, we've tended to focus our efforts in the wrong place. . . . We have tended to assume that because estrogen is a hormonal thing, a women's thing, there's nothing we can do about it except say, 'Oh dear, oh my.' In fact, what we now know is that a number of environmental chemicals can act like estrogens."

The EPA at a Standstill

The case against estrogenic pesticides isn't conclusive, but some scientists believe it's far enough along to justify special action by the agency responsible for protecting Americans from unsafe pesticides: the EPA.

There are two controversies associated with the EPA's performance on pesticides and breast cancer.

First, the agency doesn't screen pesticides for estrogenicity, or impose restrictions on pesticides that have been identified as estrogenic by someone else.

Second, after debating the issue for almost a decade, EPA officials haven't decided what to do about pesticides that have been proven to cause breast cancer in rats.

In both cases, the agency's position is rooted in what the EPA says is a lack of solid scientific information about how estrogenic chemicals actually cause cancer.

'The more I read about the breast cancer issue, the more confused I get. It's clear that the experts are all over the map as to what's causing breast cancer.'

—John McCarthy, chief scientist, National Agricultural Chemicals Association



The notion that estrogen could be a pathway to cancer is an entirely new one for the EPA, which is much more familiar with the conventional idea that chemicals cause cancer by directly attacking genes. And there are other complications, too, including uncertainty over whether breast tumors in rats are comparable to human breast cancer.

"We just don't understand what the hormonal mechanism is, so the agency is really in a quandary as to what the heck we do about this," said one EPA toxicologist, who asked not to be identified.

The EPA's stance dismays some researchers and activists, many of whom advocate a phase-out of all chlorinated organic chemicals, a huge family of compounds that includes most of the known synthetic estrogens.

"What we've seen so far from the EPA is very discouraging," said Theo Colburn, a World Wildlife Fund biologist. "We have got to get into a preventive mode and begin looking for these [hormonal] effects ahead of time, instead of waiting until it's too late and these products are already in the environment."

Other scientists say the regulatory focus should be on pesticides that are used on food crops, particularly those that are attracted to fatty tissue and can build up in body fat over decades.

"If you've got a chemical that bioaccumulates and is estrogenic, then I think you have to think very hard about whether you want to put it on the market and for what reason," said Ana

Soto, a cell biologist at Tufts University who developed one of the first estrogenicity screening tests. "No one is talking about getting rid of all these chemicals and going back to the Middle Ages, but rather to be able to detect problems before we release these chemicals into the environment."

Davis agrees. "Something that is estrogenic, attracted to fat and stored in the body, ought to be treated very strictly and probably ought not to be used unless it is for a critical national purpose and there is no substitute," she said.

At the very least, some researchers say, the EPA should require that all pesticides be systematically screened to see if they are estrogenic.

"From the standpoint of public health, I think it's very important to know" which are estrogenic, said McLachlan, the scientific director of the National Institute of Environmental Health Sciences.

Screening pesticides to see if they are estrogenic is not particularly expensive or complicated, according to Soto and others who have developed the techniques. The cost to manufacturers would be far less, they say, than that of the health and safety tests the EPA already requires.

But agency officials argue that the scientific evidence is not yet strong enough to justify screening and special restrictions.

"It would be nice to know" which pesticides are estrogenic, said Penelope

Fenner-Crisp, chief of the health effects division in the EPA's pesticides office. "But you've got to remember that we don't have free license to tell people to go out and generate data just because something's titillating our intellect."

In addition, the EPA and the pesticide industry say special rules aren't needed because the EPA already requires testing on rats and mice. If a pesticide is estrogenic, they say, the effects presumably would be detectable through such symptoms as unusual organ weights, reproductive disorders, and breast, testicular or uterine tumors.

"Even though we don't do estrogenic screening, we would pick up whether or not there's estrogenic activity through the basic pathology that we do on these animals," said McCarthy, of the industry trade group.

Under EPA rules, pesticide manufacturers are required to test their products on 50 mice and 50 rats over a two-year period, and to compare the results to a similarly sized control group. If anything unusual is found in the animals, the manufacturer is supposed to report it to the EPA, which then calculates the risk that the pesticide poses to people and the natural environment. Balancing that calculation against the economic benefits of a pesticide, the agency then decides whether to ban it, restrict it to certain doses or crops, or certify it can be used without restriction.

That's the way the process is supposed to work anyway.

But when the health issue posed by a pesticide is breast cancer, EPA records show, the agency has been unable to make a decision. And under federal law, when the EPA doesn't decide, pesticides can stay in the marketplace.

Records obtained by Newsday under the Freedom of Information Act show that the EPA has designated only 10 chemicals as breast carcinogens in rats, and not one has been banned or restricted on that basis. Four have been banned or withdrawn for other reasons and the agency is still trying to figure out what to do about the other six.

In fact, while the EPA has identified only 10 pesticides as breast carcinogens in rats, the actual number may be higher.

The National Toxicology Program,

Another Target: Electromagnetics

By Dan Fagin

STAFF WRITER

There's another mainstay of the industrial age, besides estrogenic chemicals, that is getting increasing attention in breast cancer research: electromagnetic fields.

Reported associations with childhood leukemia and brain tumors have gotten more attention, but electromagnetic fields have been inconclusively linked to breast cancer in at least four epidemiological studies.

And unlike links to leukemia and brain cancer, there is a biologically plausible explanation for an association with breast cancer.

The explanation is estrogen, the common thread that ties together all of breast cancer's known risk factors except family history.

Scientists know that melatonin, a hormone manufactured during nighttime darkness by the pineal gland in the brain, plays a key role in inhibiting production of estrogen. They also know that sustained exposure to electric fields, or to light during night hours, interrupts melatonin production. When melatonin levels are depressed, estrogen levels rise.

gen levels rise.

"Nobody can imagine how this would work for leukemia and brain cancer, but with breast cancer we have the estrogen pathway, and it makes a lot of sense," said Scott Davis, an epidemiologist at University of Washington at Seattle.

Studies have consistently shown that when rats are fed a carcinogenic chemical and then exposed to constant light or to electric fields, they develop breast tumors faster and more frequently than rats that are fed the chemical but not exposed to the fields.

And laboratory research has shown that when melatonin is added to human breast cells in a Petri dish, cell proliferation slows dramatically.

What's still lacking is solid evidence of an association between electromagnetic fields and human breast cancer.

At least four studies have found some evidence of higher-than-expected rates of male breast cancer among electric power workers, telephone linemen and electricians. Male breast cancer is extremely rare, so it's easier to notice deviations from the normal rate, and is thus easier to study.

On the other hand, those studies were all relatively small, and did not try to factor out other risks such as age or alcohol use. And several other studies that have looked for links between use of electric blankets or electric bed heaters and breast cancer have found no association.

By far the biggest and best-designed study on the subject was launched this summer in Seattle. With a \$3 million grant from the National Cancer Institute, Scott Davis is surveying 800 local women with breast cancer, and 800 healthy women who closely resemble them in age, childbearing history and other known risk factors for breast cancer.

Light and electric fields will be measured inside each of the women's bedrooms, and so will appliances and power lines near their homes. Some of the women will carry meters to measure their exposures throughout the day.

By next summer, Davis said, he hopes to have completed the measurements and begun looking for associations between electric field exposures and breast cancer risk. "We're going to see if the relationship is really there," he said.

Link to Cancer

for example, has identified at least five additional pesticides that cause breast cancer in rats, after testing a few dozen of the more than 700 pesticides on the market. That program is conducted by federal researchers at the National Cancer Institute and the National Institute of Environmental Health Sciences.

The reason the EPA may be overlooking some pesticides is that the agency, unlike the National Toxicology Program, relies on a particular type of rat called the Sprague Dawley that has a naturally high rate of breast cancer. As some agency toxicologists privately acknowledge, that means many chemicals that may cause breast cancer may have been missed by the EPA because it's difficult to tell if a chemical is raising the rat's naturally high rate of breast cancer even higher.

And there's another piece of evidence that the EPA may be overlooking some breast carcinogens. Most of the information on the cancer risks of pesticides comes from manufacturers or from the EPA evaluation of their tests. But for industrial chemicals that are not pesticides, most of the testing is done by other federal and academic research-

More than 70 million pounds of the weed-killer will be used this year, mostly on corn, grains, fruit, and occasionally lawns. Atrazine is now regularly turning up in rivers and streams in the Midwest, and scientists studying a corn-growing region of northern Italy have reported that women exposed to atrazine are twice as likely to get ovarian cancer.

Why is it taking so long for the agency to figure out what to do about atrazine and the other pesticides linked to breast cancer?

A lot of reasons, EPA officials say.

The most fundamental explanation is that while the EPA occasionally moves swiftly when the evidence is overwhelming, the agency typically takes years to make any regulatory decision.

"Obviously, the program has taken a terrible beating on the speed of the review process," said the EPA's Fenner-Crisp. "Unfortunately, we have some examples of it taking a decade or more."

But agency officials say there are other issues that are unique to breast cancer: reliance on a rat that has high background levels of breast cancer, and uncertainty over whether estrogenic effects in rats are comparable to people.

When a pesticide induces tumors in some other organ of the rat — the liver or stomach, say — that discovery typically is a major factor when the agency decides how to regulate the pesticide. The EPA generally assumes that if a pesticide causes cancer in rats, it also poses a risk to people, because most carcinogenic pesticides are thought to cause cancer by damaging genes —

a route to cancer that is relatively well understood, and thought to be similar in people and rats.

But the EPA has been at a loss over what to do about the breast tumor results in rats because those cancers are thought to be caused by an estrogen-related process that's poorly understood, and might not be comparable to humans.

Another complication is that if estrogen is the path from pesticide exposure to breast cancer, some scientists believe there may be a minimum threshold of exposure to the chemical that must be exceeded before there is significant cancer risk. Ciba-Geigy is currently trying to prove to the EPA that a hormonal threshold exists for atrazine, although so far the agency has not accepted that view.

"You can't just do a simple extrapolation and say that since you found tumors in the rat, you're going to find them in humans," said Darrell Sumner, a toxicologist with Ciba-Geigy. Except for the Sprague Dawley rat, he said, breast tumors have not been found in any other animals exposed to atrazine. And there's laboratory evidence that atrazine may actually suppress estrogen production instead of stimulating it, he said.

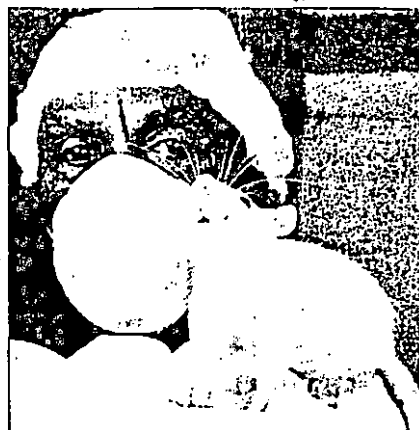
The issues are so complex that a year ago, the EPA convened a special panel of outside scientists to look at the question of whether the breast tumors in the Sprague Dawley rat are really comparable to human breast cancer.

However, that panel has met only three times in the past year, and its members say a final report may not be issued for several more years. And even when the report is finally issued, the panel is unlikely to take a firm position on the question.

"We're really stuck, because we're just beginning to learn about the mechanisms that lead to cancer," said Hugh Spitzer, associate director of the Institute of Life Sciences International, the nonprofit group the EPA hired to direct the panel's work.

But despite all the uncertainties, Spitzer argues that scientists ought to assume that the rat is a good surrogate for people unless proven otherwise. "Until you can lay out the very definitive differences, you shouldn't walk away from these tumors. I feel very strongly about that."

Tuesday: Pesticides, breast cancer and Long Island's drinking water.



Newsday / Jim Peppier

A female Sprague Dawley rat

Now, Some Smell a Rat

A white rat that tends to get breast cancer is at the center of the debate over what to do about pesticides linked to the disease.

The rat is called the Sprague Dawley, and its pedigree is so classy that the nation's research laboratories buy them by the thousands — spending about \$5 to \$7 per rat.

The Sprague Dawley is prized by cancer researchers because it has been meticulously bred to be extremely sensitive to carcinogenic chemicals, which means scientists don't have to test huge numbers of rats before they know whether a chemical causes cancer.

Just as important, the rats tend not to get tumors unless they are exposed to a carcinogen. If they're left alone, they stay healthy.

Those two qualities have helped make the Sprague Dawley the most commonly used rat in laboratory research, and a mainstay of the U.S. Environmental Protection Agency's pesticide testing program.

But there's a problem with the rat: breast cancer. Even if they aren't exposed to a cancer-causing chemical, about half the female rats will develop breast cancer before they die.

That hasn't been much of an issue in the past; researchers generally have paid little attention to breast cancer in animals, focusing instead on liver, stomach and other kinds of tumors. For most of those other cancers, the Sprague Dawley has usually been considered a good surrogate for humans.

But as evidence begins to surface linking pesticide exposures to breast cancer, EPA officials are realizing that hundreds of pesticide evaluations that are based on tests in Sprague Dawley rats might not tell the whole story.

On the one hand, the Sprague Dawley may not be a good predictor of human breast cancer risk because the rat is so prone to breast tumors, and that's one reason the EPA hasn't been able to decide whether to slap restrictions on pesticides that cause tumors in the rat.

"There just is not sufficient evidence to know how good a model the Sprague Dawley is for understanding human breast cancer," said David Neumann of the Institute of Life Sciences International, a nonprofit scientific group that is studying the issue for the EPA.

But on the other hand, the EPA may have overlooked many carcinogenic chemicals because it's so difficult to tell whether a chemical exposure is raising the number of breast tumors beyond an already high background level.

"Generally, the breast tumors have been disregarded as an effect because the background level is so high you can't tell what's going on," said one agency scientist, who asked not to be identified.

Switching to a different kind of rat has never been considered, he said, because hundreds of pesticides would then have to be retested.

—Dan Fagin



'The environmental hypothesis is extremely interesting and scientifically important, and we're going to pursue it. This is an area that is certainly high priority.'

—Dr. Samuel Broder, director, the National Cancer Institute

ers. And those studies have found that breast tumors are a pervasive result of chemical exposures.

At least 68 non-pesticide chemicals — many of them structurally similar to pesticides — have been identified by federal or private researchers as causing breast cancer in lab animals, according to lists compiled by and for Newsday. That's more chemicals than have been linked to any other kind of cancer except liver, lung and stomach.

In the few cases when the EPA has concluded that a pesticide causes breast cancer in rats, the agency has not acted on the information.

Of the 15 pesticides that have been identified so far as causing breast cancer in rats, several have been banned or withdrawn — but always for other reasons. This group includes four of the EPA-identified pesticides: captan, propazine, terbutryn and Savay. And it also includes all five of the pesticides identified by the National Toxicology Program: 1,2-dichloropropane, 1,2-dibromo-3-chloropropane (DBCP), 1,2-dichloroethane, sulfallate and 1,2-dibromoethane (EDB).

But six other pesticides that the EPA has officially designated as breast carcinogens in rats remain on the market: atrazine, cyanazine, express, oryzalin, simazine and terrazole. And only atrazine and simazine face any restrictions at all. Both can be applied on farms only by certified pesticide applicators, although homeowners are still free to use them without restriction.

Because it's so widely used, atrazine is perhaps the most striking example of the EPA's indecisiveness on breast cancer.

It's been nine years since the agency learned that atrazine causes breast tumors in rats, the pesticide's only known carcinogenic effect, EPA records show. Those tests were conducted by a firm hired by atrazine's manufacturer, Ciba-Geigy Corp., and EPA memos indicate the agency considered those tests particularly persuasive because they showed that the higher the dose of atrazine, the more likely a rat was to get breast cancer. By 1988, the EPA had formally declared atrazine a mammary carcinogen in rats, and a possible human carcinogen.

But today, the EPA still hasn't decided what to do about atrazine. And while the agency has been pondering the issue, atrazine has become the best-selling pesticide in the United States.