Agent Orange and Cancer

About 3 million Americans served in the armed forces in Vietnam and nearby areas during the 1960s and early 1970s, the time of the Vietnam War. During that time, the military used large amounts of mixtures known as *defoliants,* which are chemicals that cause the leaves to fall off plants. One of these defoliants was Agent Orange, and some troops were exposed to it. Many years later, questions remain about the lasting health effects of those exposures, including increases in cancer risk.

This article offers a brief overview of the link between Agent Orange and cancer. It does not offer a complete review of all evidence – it is meant to be a brief summary. It also includes some information on benefits for which Vietnam veterans exposed to Agent Orange may be eligible.

Some background on Agent Orange

During the Vietnam War, US military forces sprayed millions of gallons of herbicides (plant-killing chemicals) on lands in Vietnam, Laos, and other nearby areas to remove forest cover, destroy crops, and clear vegetation from the perimeters of US bases. This effort, known as Operation Ranch Hand, lasted from 1962 to 1971.

Different mixes of herbicides were used, but most were mixtures of 2 chemicals that were phenoxy herbicides:

- 2,4-dichlorophenoxyacetic acid (2,4-D)
- 2,4,5-trichlorophenoxyacetic acid (2,4,5-T)

Each mixture was shipped in a chemical drum marked with an identifying colored stripe. The most widely used mixture contained equal parts 2,4-D and 2,4,5-T. Because this herbicide came in drums with orange stripes, it was called Agent Orange. Today, Agent Orange refers generally to all the phenoxy herbicides sprayed at the time. (Other types of herbicides were also used, including cacodylic acid and picloram.)

The 2,4,5-T in Agent Orange was contaminated with small amounts of dioxins, which were created unintentionally during the manufacturing process. Dioxins are a family of dozens of related chemicals. They can form during the making of paper and in some other industrial processes. The main dioxin in Agent Orange, 2,3,7,8-tetrachlorodibenzo-p-dioxin, or TCDD, is one of the most toxic.

After a study in 1970 found that 2,4,5-T could cause birth defects in lab animals, the use of 2,4,5-T in Vietnam was stopped. A year later, all military herbicide use in Vietnam ended. During the 1970s, some veterans returning from Vietnam began to report skin rashes, cancer, psychological symptoms, birth defects in their children, and other health problems. Some veterans were concerned that Agent Orange exposure might have contributed to these problems. These concerns eventually led to a series of scientific studies, health care programs, and compensation programs directed to the exposed veterans.

A large class-action lawsuit was filed in 1979 against the herbicide manufacturers, and was settled out of court in 1984. It resulted in the Agent Orange Settlement Fund, which distributed nearly $200 million to veterans between 1988 and 1996.

Although there is now quite a bit of evidence about the health effects of Agent Orange, many questions have not yet been answered.

How were people exposed to Agent Orange?

About 3 million people served in the US military in Vietnam during the course of the war, about 1.5 million of whom served during the period of heaviest herbicide spraying from 1967 to 1969.

In studies comparing Vietnam veterans with veterans who had served at the same time elsewhere, blood TCDD (dioxin) levels were found to be higher among those who had served in Vietnam, although these levels went down slowly over time.

Exposure to Agent Orange varied a great deal. Most of the large-scale spraying in Operation Ranch Hand was done with airplanes and helicopters. However, some herbicides were sprayed from boats or trucks, and some were applied by soldiers with backpack sprayers. Those who loaded airplanes and helicopters might have been exposed the most. Members of the Army Chemical Corps, who stored and mixed herbicides and defoliated the perimeters of military bases, probably also had some of the heaviest exposures. Others with potentially heavy exposures included members of Special Forces units who defoliated remote campsites, and members of Navy river units who cleared base perimeters.

Exposures could have occurred when the chemicals were breathed in, ingested in contaminated food or drink, or absorbed through the skin. Exposure may have been possible through the eyes or through breaks in the skin, as well.

One of the challenges in assessing the health effects of Agent Orange exposure has been determining how much any individual veteran was exposed to (or even what they were exposed to), as very little information of this type is available.

Does Agent Orange cause cancer?

Researchers use 2 main types of studies to try to determine if a substance or exposure causes cancer.

One type of study looks at cancer rates in different groups of people. Such a study might compare the cancer rate in a group exposed to a substance versus the rate in a group not exposed to it, or compare it to what the expected cancer rate would be in the general population. But studies of people can sometimes be hard to interpret, because other factors that are hard to account for might be affecting the results.

In studies done in the lab, animals are exposed to a substance (often in very large doses) to see if it causes tumors or other health problems. Researchers may also expose normal cells in a lab dish to the substance to see if it causes the types of changes that are seen in cancer cells. In these types of studies, other factors are easier to control for, but it's not always clear if the results in lab dishes or animals would be the same in humans, for a number of reasons.

In most cases neither type of study provides definitive evidence on its own, so researchers usually look at both human and lab-based studies when trying to determine if something might cause cancer.

Studies in people

Studies of Vietnam veterans provide some of the most direct evidence of the health effects of Agent Orange exposure.

The Centers for Disease Control and Prevention (CDC), the US Air Force, and the Department of Veterans Affairs (VA) have conducted studies in thousands of Vietnam veterans. However, most of these studies have been limited by the fairly small number of people who were highly exposed to Agent Orange. About a dozen states have also conducted studies of their veterans, and some of them have yielded cancer risk information. A series of studies of Australian Vietnam veterans has also provided some information on cancer risk.

Because of the limits of the Vietnam veteran studies, studies of 3 other groups have provided important information on the potential cancer-causing properties of Agent Orange exposure:

- Vietnamese soldiers and civilians exposed to the same herbicides as United States service personnel, often for more prolonged periods (although there have been few thorough health studies in these populations)
- Workers exposed to herbicides in other settings, such as herbicide manufacturing workers, herbicide applicators, farmers, lumberjacks, and forest and soil conservationists, who often had much higher blood dioxin levels than Vietnam veterans
- People exposed to dioxins after industrial accidents in Germany, Seveso (Italy), and California, and after chronic exposures at work and in the environment

Each of these groups differs from the Vietnam veterans in the characteristics of the people exposed, the nature of the dioxin exposures, and other factors such as diet and other chemical exposures.

Taken together, these studies have looked at possible links between Agent Orange (or dioxin) and a number of cancer types.

Soft tissue sarcoma: Most studies in Vietnam veterans have not found an increase in soft tissue sarcomas. However, soft tissue sarcomas have been linked to phenoxy herbicide exposure in a series of studies in Sweden and in some studies of industrially exposed workers. Many studies of farmers and agricultural workers show an increase in soft tissue sarcomas, which may relate to herbicide exposure. Soft tissue sarcomas have also been linked to dioxin exposure in some chemical manufacturing workers and in some other workplace studies.

Non-Hodgkin lymphoma: Most studies of Vietnam veterans have not shown an increase in non-Hodgkin lymphoma (NHL). But several studies have found a link between phenoxy herbicide exposure (usually on the job) and NHL. Some studies of farmers and agricultural workers also suggest this association, although not all studies have found such a link.

Hodgkin disease: Most studies of Vietnam veterans have not found an increase in Hodgkin disease. However, Hodgkin disease has been linked to phenoxy herbicide exposure in some other studies. Many studies of farmers and agricultural workers show an increase in Hodgkin disease, which may relate to herbicide exposure.

The link between Hodgkin disease and dioxin exposure specifically is less clear, as studies have given mixed results.

Lung and other respiratory cancers: Most studies of Vietnam veterans have not shown an increase in respiratory cancers, such as those of the lung, trachea (windpipe), and larynx (voice box). Most studies of people exposed to herbicides at work, such as herbicide manufacturing workers, herbicide applicators, and farmers have not found an excess risk of lung cancer.

Most studies of groups of people highly exposed to dioxin after industrial accidents have not found an increase in respiratory cancers. However, chronic exposures to high levels of dioxin in the workplace have been linked with increased risk of respiratory cancers in some studies.

Prostate cancer: Most studies of Vietnam veterans have not found an excess risk of prostate cancer, but results from a few studies have suggested a possible link. For example, a recent study in veterans found that exposure to Agent Orange was linked to an increased risk of developing more aggressive forms of prostate cancer.

Studies of other groups have also yielded mixed results. Most studies of people exposed to phenoxy herbicides at work do not show an excess of prostate cancer. However, some studies have found a small excess risk of prostate cancer related to dioxin exposure.

Multiple myeloma: Most studies of Vietnam veterans have had too few cases of multiple myeloma (a type of immune system cancer that affects the bones) to be helpful in determining if there is a risk.

However, other studies of people exposed to pesticides, herbicides, and/or dioxins have suggested a possible link. Several studies of farmers and agricultural workers have reported a small increase in risk of multiple myeloma, although some studies show no excess risk.

Gastrointestinal (GI) cancer: Cancers of the GI system – esophagus, stomach, liver, pancreas, colon, and rectum – have been extensively studied in Vietnam veterans, groups with herbicide exposure in the workplace, and people exposed to dioxins. Most of these studies have not found a link between these exposures and any GI cancer.

Brain tumors: Most studies have not found a link between Vietnam service, workplace herbicide exposure, or dioxin exposure, and brain tumors.

Breast cancer: As most Vietnam veterans are men, in whom breast cancer is very rare, few studies have looked for possible links between Agent Orange and breast cancer. Some studies looking at exposure to dioxin in the workplace or from industrial accidents have noted a possible link, but others have not, so more research is needed in this area.

Other cancers: Few studies have looked at a possible link between Agent Orange exposure and other cancers, including cancers of the nose and nasopharynx (upper part of the throat), cervix, endometrium (uterus), ovaries, liver and bile ducts, bone, kidneys, bladder, testicles, or skin, or leukemias other than chronic lymphocytic leukemia (in veterans themselves, as opposed to their children).

Leukemia and other cancers in the children of veterans: A few studies have pointed to a possible link between a father's exposure to Agent Orange or other herbicides and leukemia in his children. But several other studies have not found links with leukemia or other childhood cancers.

Studies done in the lab

Herbicides such as 2,4,5-T and 2,4-D are not considered highly toxic compounds by themselves, and high doses are needed to cause effects in lab animals. These compounds have not been linked with cancer in animal studies.

In the lab, TCDD (dioxin) increases the risk of a wide variety of tumors in rats, mice, and hamsters. In lab dish studies, it has been shown to alter which genes are turned on or off and affect how cells divide and die, all of which could affect cancer risk.

What the expert agencies say

Several agencies (national and international) study different substances in the environment to determine if they can cause cancer. (A substance that causes cancer or helps cancer grow is called a *carcinogen*.) The American Cancer Society looks to these organizations to evaluate the risks based on evidence from laboratory, animal, and human research studies.

Some of these expert agencies have looked at whether Agent Orange or related compounds can cause cancer.

Institute of Medicine

Since 1994, the federal government has directed the Institute of Medicine (IOM), part of the National Academy of Sciences (NAS), to issue reports every 2 years on the health effects of Agent Orange and similar herbicides. Titled *Veterans and Agent Orange*, the IOM reports assess the risk of both cancer and non-cancer health effects. Each health effect is categorized as having one of the following:

- Sufficient evidence of an association
- Limited/suggestive evidence of an association

- Inadequate/insufficient evidence to determine whether an association exists
- Limited/suggestive evidence of *no* association

This framework provides a basis for government policy decisions in the face of uncertainty. As of the most recent update (2012), the links between Agent Orange exposure and cancer were designated as shown. (Note that this table shows only cancers. Other health effects are listed in the next section.)

IOM: Links Between Herbicides (Including Agent Orange) and Cancer

Sufficient evidence of an association

Soft tissue sarcoma

Non-Hodgkin lymphoma (NHL)

Hodgkin disease

Chronic lymphocytic leukemia (CLL), including hairy cell leukemia and other chronic B-cell leukemias

Limited/suggestive evidence of an association

Respiratory cancers (lung, trachea, bronchus, larynx)

Prostate cancer

Multiple myeloma

Inadequate/insufficient evidence to determine whether an association exists

Mouth, throat, and sinus cancers

Gastrointestinal cancers (esophagus, stomach, pancreas, colon, rectum)

Liver, gallbladder, and bile duct cancers

Bone and joint cancers

Skin cancers

Breast cancer

Female reproductive cancers (cervical, ovarian, endometrial, uterine sarcoma)

Testicular and penile cancers

Bladder cancer

Kidney cancer

Brain tumors

Cancers of endocrine glands (thyroid, thymus, etc.)

Leukemia (other than CLL and hairy cell leukemia)

Cancers at all other sites

Cancer (including leukemia) in the children of veterans

National Toxicology Program

The US National Toxicology Program (NTP), formed from parts of several government agencies, evaluates exposures that may be carcinogenic (cancer-causing).

The NTP has not classified the phenoxy herbicides, including Agent Orange, but it lists 2,3,7,8-TCDD (dioxin) as "known to be a human carcinogen."

International Agency for Research on Cancer

The International Agency for Research on Cancer (IARC) is part of the World Health Organization (WHO). Its major goal is to identify causes of cancer.

IARC has not rated Agent Orange itself, but it classifies the phenoxy herbicides, including 2,4-D and 2,4,5-T, as "possibly carcinogenic to humans." It lists 2,3,7,8-TCDD (dioxin) as "known to be carcinogenic to humans."

Environmental Protection Agency

The US Environmental Protection Agency (EPA) maintains the Integrated Risk Information System (IRIS), an electronic database that has information on human health effects from exposure to substances in the environment. The EPA is now reviewing whether 2,3,7,8-TCDD (dioxin) is carcinogenic to humans.

(For more information on the classification systems used by the NTP, IARC, and EPA, see our document, *Known and Probable Human Carcinogens*.)

Does Agent Orange cause any other health problems?

Vietnam service, and Agent Orange exposure in particular, have also been studied for possible links to health problems other than cancer.

In its report *Veterans and Agent Orange*, the Institute of Medicine has looked at the possible link between exposure to Agent Orange and other herbicides and several non-cancerous health conditions.

IOM: Links Between Herbicides (Including Agent Orange) and Other Health Effects

Sufficient evidence of an association

Chloracne

Limited/suggestive evidence of an association

Amyloidosis
Early-onset peripheral neuropathy
Parkinson disease
Porphyria cutanea tarda
High blood pressure
Stroke
Ischemic heart disease
Type 2 diabetes
Spina bifida in children of veterans

Chloracne is an acne-like rash caused by exposure to high levels of chlorine-containing chemicals.

Amyloidosis is a condition in which abnormal proteins build up in different tissues and organs in the body.

Early-onset peripheral neuropathy is a condition that starts soon (within a year) after exposure, in which damage to nerves outside the brain and spinal cord causes symptoms such as numbness or tingling in the hands and feet.

Porphyria cutanea tarda (PCT) is a condition that can result in liver damage and blistering of the skin when exposed to light.

Spina bifida is a type of birth defect in which some of the bones of the spine do not form completely before birth.

Concerns have also been raised about other conditions in exposed veterans, including psychiatric illnesses and other nervous system problems, asthma, immune system disorders, digestive diseases, infertility, and birth defects other than spina bifida. According to the Institute of Medicine, there isn't enough evidence at this time to determine if there is a link between these conditions and Agent Orange.

Benefits for exposed veterans

Vietnam veterans and those who served at certain other locations (such as Thailand or the Korean Demilitarized Zone) who were exposed to Agent Orange or other herbicides may be eligible for 3 kinds of benefits.

Because past Agent Orange exposure is hard to prove, the Department of Veterans Affairs (VA) presumes that all veterans who served in certain locations at certain times might have been exposed. For example, if a veteran served in Vietnam between 1962 and 1975 and becomes disabled with one of the conditions designated as Agent Orange-related, the VA classifies his or her disability as service-related. To learn more about who might be eligible for the benefits below, call the Department of Veterans Affairs at 1-800-749-8387 or visit their website at www.publichealth.va.gov/exposures/agentorange/militaryexposure.asp.

Agent Orange Registry health exam

The Agent Orange Registry is a program administered by the VA since 1978. Veterans who qualify and participate in this program receive free medical exams, lab tests, and specialty referrals if appropriate. Veterans are not required to enroll in the VA health care system to receive the registry exam.

Disability compensation

Disability compensation payments are available for veterans with service-related illnesses or illnesses that were incurred or aggravated by military service. The amount of the monthly payment is determined by the extent of disability.

The diseases considered related to Agent Orange exposure correspond closely to the conditions found by the IOM to have "sufficient" or "limited/suggestive" evidence of an association. The cancers on the list include:

- Hodgkin disease
- Multiple myeloma
- Non-Hodgkin lymphoma
- Prostate cancer
- Cancer of the lung, bronchus, larynx (voice box), or trachea (windpipe)
- Soft tissue sarcoma (other than osteosarcoma, chondrosarcoma, Kaposi sarcoma, or mesothelioma)
- Chronic lymphocytic leukemia, hairy cell leukemia, and other chronic B-cell leukemias

Conditions other than cancer on this list include peripheral neuropathy, amyloidosis, chloracne, type 2 diabetes, ischemic heart disease, Parkinson disease, and porphyria cutanea tarda. Also included are spina bifida and certain other birth defects in the children of veterans.

Medical benefits

Some veterans qualify for medical care after being exposed to Agent Orange. The VA provides medical care at VA facilities, prescription medicines, and home health and hospice care to veterans with conditions linked with herbicide exposure in Vietnam. These include the cancers and other health conditions presumed to be Agent Orange-related, as listed before.

Veterans might want to check the VA web site (www.publichealth.va.gov/exposures/agentorange) or their local VA hospitals for more information on any of these Agent Orange-related benefits.

Other things you can do for your health

Be sure your doctor knows if you have a history of Agent Orange exposure. Because of the possibility of excess cancer risk, your doctor may advise you to get cancer screening tests and to see your doctor promptly if you have suspicious symptoms.

Of course, veterans are at risk for many types of cancer just like everyone else, even if they have not been exposed to Agent Orange. You might be able to lower your risk of cancer (and other diseases) by quitting smoking, staying at a healthy weight, getting regular physical activity, eating a healthy diet, and avoiding exposure to other environmental carcinogens.

If you are concerned about past exposure to Agent Orange, you may want to join a support group online or through your local VA hospital. You might also want to consult an occupational and environmental medicine clinic. These clinics can help assess past exposures and any risk that may persist, and can recommend appropriate steps to help you protect your health. You can look for clinics near you by visiting the Association of Occupational and Environmental Clinics at www.aoec.org.

To learn more

More information from your American Cancer Society

Here is more information you might find helpful. You also can order free copies of our documents from our toll-free number, 1-800-227-2345, or read them on our website, www.cancer.org.

Known and Probable Human Carcinogens

National organizations and websites

In addition to the American Cancer Society, other sources of information and support include*:

Department of Veterans Affairs
Toll-free number: 1-800-749-8387
Home page: www.va.gov
Information on Agent Orange: www.publichealth.va.gov/exposures/agentorange

Vietnam Veterans of America
Toll-free number: 1-800-882-1316 (1-800-VVA-1316)
Home page: www.vva.org
Information on Agent Orange: www.vva.org/Committees/AgentOrange/index.html

Institute of Medicine
Home page: www.iom.edu
Veterans and Agent Orange - Update 2012: www.iom.edu/Reports/2013/Veterans-and-Agent-Orange-Update-2012.aspx

Association of Occupational and Environmental Clinics
Website: www.aoec.org

**Inclusion on this list does not imply endorsement by the American Cancer Society*

No matter who you are, we can help. Contact us anytime, day or night, for information and support. Call us at 1-800-227-2345 or visit www.cancer.org.

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