

## Agent Orange and Cancer: An Overview for Clinicians

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**ABSTRACT** Approximately 3 million Americans served in the armed forces in Vietnam during the Vietnam War. Some of them (as well as some Vietnamese combatants and civilians, and members of the armed forces of other nations) were exposed to defoliant mixtures, including Agent Orange. Evidence suggests some lasting health effects from these exposures, including certain cancers. This article reviews the evidence on cancer risk after Agent Orange exposure. Data sources include studies of Vietnam veterans, workers occupationally exposed to herbicides or dioxins (since dioxins contaminated the herbicide mixtures used in Vietnam), and Vietnamese populations. The article then reviews clinical issues that arise when caring for cancer patients who may have sustained Agent Orange exposure, or others concerned about such exposure to Agent Orange, such as available benefits programs and sources of information and counseling. (*CA Cancer J Clin* 2003;53:245–255.) © American Cancer Society, 2003.

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### INTRODUCTION

Approximately 3 million Americans served in the armed forces in Vietnam during the 1960s and early 1970s, the time of the Vietnam War. During that time, the military applied large amounts of defoliant mixtures, including so-called Agent Orange, with resultant exposure of some troops. To this day, three decades after US forces withdrew from Vietnam, questions remain about the lasting health consequences, including cancer risk, of those exposures among veterans. As the veteran population ages, and as epidemiologic studies continue, further evidence continues to emerge. Most recently, in early 2003, a new conclusion was reached: that Agent Orange exposure is associated with chronic lymphocytic leukemia among veterans. This decision triggered various benefits for exposed veterans with that disease.

This article offers a brief overview of the health evidence on Agent Orange and cancer, to help clinicians serve Vietnam veteran patients and their family members. The evidence comes from several sources including studies of Vietnam veterans, workers exposed to herbicides or dioxins (since dioxins contaminated the herbicide mixtures used in Vietnam) in occupational settings, and studies of health effects among Vietnamese populations in the aftermath of the war. This article does not offer a complete review of all these lines of evidence. Instead, it summarizes the evidence briefly, and introduces readers to benefits programs and other issues that arise in caring for cancer patients or others concerned about the risks from exposure to Agent Orange during military service.

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### BACKGROUND

During the Vietnam War, United States military forces sprayed nearly 19 million gallons of herbicide on approximately 3.6 million acres of Vietnamese and Laotian land 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. Various herbicide formulations were used, but most were mixtures of the phenoxy herbicides 2,4-dichlorophe-

noxyacetic acid (2,4-D) and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T). Each formulation 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 is used to refer generally to all the phenoxy herbicides sprayed at the time.<sup>1</sup> In addition to the phenoxy herbicides, other herbicides used included cacodylic acid, an organic arsenic compound, and picloram, a chlorobenzoic acid herbicide.

The 2,4,5-T was contaminated with minute amounts of dioxins as a byproduct of the manufacturing process. Dioxins are a family of biologically active chlorinated aromatic compounds formed during combustion of chlorine-containing materials, manufacturing of paper, and other processes. Because they persist for years in the environment, they form part of a group of chemicals known as “persistent organic pollutants.” The particular dioxin present in Agent Orange, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin, or TCDD, is unusually toxic. In postwar studies that compared Vietnam veterans with contemporary veterans who had served elsewhere, TCDD levels were found to be elevated among those who had served in Vietnam,<sup>2-4</sup> although the elevations diminished slowly over time.

After a scientific report in 1970 indicated that 2,4,5-T could cause birth defects in laboratory animals, the use of 2,4,5-T in Vietnam was suspended.<sup>5</sup> A year later, all military herbicide use in Vietnam ended. During the 1970s, returned Vietnam veterans began to report skin rashes, cancer, psychological symptoms, congenital anomalies and handicaps in their children, and other health problems. Some veterans were concerned that Agent Orange exposure might have contributed to these health problems. These concerns helped initiate 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, including Dow, Monsanto, Diamond Shamrock, Hercules, Uniroyal, and

others, and 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 considerable evidence available about the effects of Agent Orange exposure, large uncertainties remain.

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#### AGENT ORANGE EXPOSURE

Approximately 3 million US military personnel served in Vietnam during the course of the war, of whom about 1.5 million served during the period of heaviest herbicide spraying, 1967 to 1969. Exposure to Agent Orange varied considerably. Most of the large-scale spraying operations in Operation Ranch Hand were conducted using airplanes and helicopters. However, some herbicides were sprayed from boats and ground vehicles, and some were applied by soldiers with backpack sprayers. Ranch Hand personnel who loaded airplanes and helicopters probably sustained some of the heaviest exposures. Members of the Army Chemical Corps, who stored and mixed herbicides and defoliated the perimeters of military bases, are also thought to have had some of the heaviest exposures.<sup>4</sup> 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.<sup>6-12</sup> Exposures could have occurred through inhalation, ingestion, and skin absorption and possibly through more unusual routes such as through skin lesions and ocular absorption.

One of the challenges in assessing the health effects of Agent Orange exposure is quantifying the exposures. There is little precise information for any individual veteran, about how much exposure he or she sustained, or even to what herbicides.

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#### ASSOCIATION OF AGENT ORANGE AND CANCER

##### Human Evidence

Epidemiologic studies of Vietnam veterans potentially provide the most direct evidence of

the health effects of Agent Orange exposure. However, because of the small number of highly exposed persons, these studies yield very limited information on cancer. The Vietnam Experience Study (VES), conducted by the Centers for Disease Control (CDC),<sup>13</sup> was a historical cohort study that compared 9324 Vietnam Army veterans with 8989 Vietnam-era Army veterans who served elsewhere. It included a mortality study; health interviews; and clinical, psychological, and laboratory evaluation of a random sample of veterans who completed the health interview. The total number of cancer deaths in the VES was inadequate to yield information on specific cancer types. A related effort was the CDC Selected Cancers Study, a population-based case-control study conducted in eight cancer registries that provided data on non-Hodgkin lymphoma,<sup>14</sup> sarcomas,<sup>15</sup> and other cancers.<sup>16</sup> In all of these studies, the number of veterans with substantial exposure to Agent Orange was too small to support firm conclusions.

The Department of Veterans Affairs, formerly the Veterans Administration (VA), also conducted a series of studies beginning in the 1980s. The VA studies ranged from large-scale cohort studies<sup>17-19</sup> to case-control studies<sup>20</sup> to studies of specific subgroups of veterans.

Both the CDC and the VA studies looked broadly at Vietnam service, without a special focus on Agent Orange exposure (although some VA studies focused on Chemical Corps veterans<sup>21,22</sup>). In contrast, a third study, the Air Force Health Study, focused specifically on approximately 1200 Ranch Hand veterans directly involved in herbicide distribution and 1300 comparison veterans.<sup>23-25</sup> This 20-year prospective study, launched in 1982, involved periodic physical examinations, medical records reviews, and blood dioxin measurements. Information is available at the Air Force Research Laboratory Web site (<http://www.brooks.af.mil/AFRL/HED/hedb/afhs/afhs.html>). Although this study focused more directly on Agent Orange exposure, the relatively small number of subjects, and the even smaller number with elevated TCDD levels, greatly limited the statistical power to detect increases in cancer incidence.

At the state level, about a dozen states, mostly in the Midwest and Northeast, conducted studies of their veterans, some of which yielded cancer information (eg, New York;<sup>26</sup> Massachusetts;<sup>27</sup> Wisconsin;<sup>28</sup> Michigan<sup>29</sup>). Finally, a series of studies of Australian Vietnam veterans yielded information on cancer risk.<sup>30-33</sup> These studies, too, were limited by small sample sizes, by the absence of detailed exposure assessment, and at least initially by the relatively young age of the veteran populations. As the Vietnam veterans continue to age, additional research should yield additional information about cancer risk.

Because of the limits of the Vietnam veteran studies, indirect sources have provided important information on the potential carcinogenicity of Agent Orange exposure. One of these is data on Vietnamese soldiers and civilians exposed to the same herbicides as United States service personnel, often for more prolonged periods,<sup>34-38</sup> although there have been few systematic health studies in these populations. A second indirect source of information is workers exposed to herbicides in other settings, such as herbicide manufacturing workers,<sup>39-43</sup> herbicide applicators,<sup>44</sup> farmers,<sup>45</sup> lumberjacks,<sup>46</sup> and forest and soil conservationists,<sup>47</sup> who often had much higher serum dioxin levels than Vietnam veterans. Third, people exposed to dioxins after industrial accidents in Germany,<sup>48,49</sup> Seveso, Italy,<sup>50</sup> and California,<sup>51</sup> and after chronic exposures at work<sup>52-54</sup> and in the environment<sup>55</sup> have been studied. Each of these populations differs from the Vietnam veterans in demographic composition, the nature of the dioxin exposures, and other factors such as diet and concomitant chemical exposures.

Based on this relatively large body of epidemiologic evidence, conclusions can be drawn about several cancers. Each of these is discussed in the paragraphs that follow.

#### *Soft Tissue Sarcoma*

Studies of Vietnam veterans have not demonstrated an increase in soft tissue sarcomas. In particular, no association with soft tissue sarcoma was seen in the Ranch Hand study,<sup>24</sup> in a study of 10,716 Marines who had served in

Vietnam,<sup>18</sup> a large case-control study of sarcoma patients in VA hospitals,<sup>56</sup> the Selected Cancers Study,<sup>15</sup> or studies of veterans in Michigan,<sup>29</sup> Massachusetts,<sup>27</sup> or other states. A study of Australian Vietnam veterans suggested a large increase in soft tissue sarcomas, but this finding was based on a mail survey of self-reported diagnoses.<sup>32</sup> In a follow-up study designed to validate the diagnoses, the excess of soft tissue sarcomas could not be verified.<sup>33</sup>

However, soft tissue sarcomas have been linked to phenoxy herbicide exposure by a series of case-control studies in Sweden<sup>57,58</sup> and by cohort<sup>39,40</sup> and case-control<sup>41</sup> 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 a study of 5132 chemical manufacturing workers in the United States,<sup>53</sup> in some other occupational studies,<sup>59</sup> and in some studies of environmental exposures.<sup>60</sup>

#### *Non-Hodgkin Lymphoma*

Most studies of Vietnam veterans have not demonstrated an increase in non-Hodgkin lymphoma (NHL). The Selected Cancers Study showed that Vietnam service was associated with a 50% increased risk of NHL, but self-reported Agent Orange exposure was not associated with increased risk.<sup>14</sup> Similarly, in the CDC's Vietnam Experience Study, there were seven NHL deaths among the 8,170 Vietnam veterans and only one NHL death among the 7,564 non-Vietnam veterans. Based on military job titles, there was no suggestion that the seven Vietnam veterans with NHL had sustained Agent Orange exposure.<sup>61</sup> In contrast, the Ranch Hand study showed no increase in NHL,<sup>62</sup> nor did the VA mortality study of 33,833 Army and Marine Vietnam veterans,<sup>19</sup> a case-control study of 201 Vietnam veterans with NHL,<sup>63</sup> or numerous state-level studies. A study of Australian Vietnam veterans suggested a large increase in NHL, but this finding was based on a mail survey of self-reported diagnoses.<sup>32</sup> In a validation study that attempted to confirm the diagnoses, the num-

ber of NHL cases declined to the upper end of the expected range.<sup>33</sup>

Several case-control studies have found an association between phenoxy herbicide exposure (usually on the job) and NHL.<sup>64-67</sup> Numerous other studies of farmers and agricultural workers also suggest this association, although cohort studies of herbicide production workers have generally been negative or report nonsignificant associations based on very small numbers of cases. Dioxin exposure was not associated with NHL in either the NIOSH occupational study<sup>54</sup> or the Seveso follow-up,<sup>50</sup> although a recent study of a dioxin-exposed area near a municipal solid waste incinerator in France<sup>60</sup> suggested a small increase in NHL.

#### *Hodgkin Disease*

Studies of Vietnam veterans have not demonstrated an increase in Hodgkin disease. In particular, the Ranch Hand study did not show an increase in these tumors,<sup>62</sup> nor did a study of 33,833 Army and Marine Vietnam veterans,<sup>19</sup> the Selected Cancers Study,<sup>16</sup> a case-control study of 283 Vietnam-era veterans with Hodgkin disease,<sup>68</sup> or studies of veterans in Michigan,<sup>29</sup> New York,<sup>26</sup> or other states.

However, Hodgkin disease was linked to phenoxy herbicide and chlorophenol exposure in one case-control study in Sweden,<sup>64,69</sup> and another yielded similar results, although without statistical significance.<sup>65</sup> 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 is less clear. The large occupational study of 5,132 chemical manufacturing workers in the United States<sup>53,54</sup> did not show an increase in Hodgkin disease. The Seveso follow-up showed no cases of Hodgkin disease in the zone of greatest dioxin exposure, and a small excess of cases in the other zones.<sup>50</sup> Other studies have given mixed results.

#### *Respiratory Cancers*

Studies of Vietnam veterans have not shown a consistent pattern of increases in respiratory

cancers (lung, trachea/bronchus, larynx). The VA studies did not reveal increased mortality from these cancers in Vietnam veterans,<sup>19,70</sup> nor did the study of Army Chemical Corps veterans.<sup>22</sup> The Ranch Hand study suggested an increase in lung cancer, with a relative risk of 3.7, but this finding was based on only 10 deaths, and a high prevalence of smoking in the Ranch Hand population may have accounted for this finding.<sup>62</sup> In studies of Australian Vietnam veterans, self-reports suggested an increase in lung cancer (120 cases versus 65 expected),<sup>32</sup> but in the validation study, only 46 of these self-reported cases could be confirmed, suggesting a deficit of lung cancer.<sup>33</sup>

Most studies of workers with occupational herbicide exposure, such as herbicide manufacturing workers,<sup>39,40,42,43</sup> herbicide applicators,<sup>44</sup> farmers,<sup>45</sup> and forest and soil conservationists<sup>47</sup> have shown no excess of lung cancer. Similarly, follow-up of the Seveso accident has not shown an association between dioxin exposure and lung cancer,<sup>50</sup> although follow-up of industrial accidents in Germany<sup>48</sup> and California<sup>51</sup> did suggest an increase in respiratory cancers, based on small numbers of cases. Chronic workplace exposures to dioxin have also been associated with increased respiratory cancer, among those with enough exposure to have developed chloracne.<sup>54</sup> Together, these data provide little support for the hypothesis that chlorophenoxy acids increase the risk of lung cancer, but they suggest a possible association of dioxin exposure with lung cancer.

#### *Prostate Cancer*

While the VA<sup>19</sup> and Ranch Hand<sup>62</sup> studies did not show an excess of prostate cancer, the Australian veterans study (AIHW) did show an excess, with 212 cases observed and 147 expected.<sup>33</sup> Studies of other groups have yielded inconsistent results. Most studies of workers occupationally exposed to phenoxyacetic acid herbicides do not show an excess of prostate cancer. However, there are exceptions. For example, recent studies of pesticide applicators in Florida (exposed to many agents other than herbicides) reported an approximate doubling of prostate cancer incidence and mortality.<sup>71,72</sup>

Follow-up of the Seveso accident revealed a nonsignificant 20% excess of prostate cancer,<sup>50</sup> as did the NIOSH study of chronic dioxin exposure.<sup>54</sup> However, follow-up of other acute dioxin exposure incidents<sup>48,51</sup> showed no excess of prostate cancer. Overall, the evidence of an association between Agent Orange and prostate cancer is not strong.

#### *Multiple Myeloma*

None of the studies of Vietnam veterans are informative regarding multiple myeloma risk, because the numbers of cases have been consistently small. However, other studies of people exposed to pesticides, herbicides, and/or dioxins have been suggestive. For example, several studies of farmers and agricultural workers have reported a small increase in multiple myeloma, although other studies show no excess of this neoplasm.<sup>73</sup> Follow-up of the Seveso accident shows a deficit of multiple myeloma among exposed males but an excess among females (relative risk 3.7 based on four cases), a disparity that remains unexplained.<sup>50</sup> Similarly, the NIOSH study of 5,132 workers exposed to dioxins showed a marginally significant doubling of multiple myeloma risk, based on 10 cases.<sup>54</sup> Overall the evidence linking Agent Orange to multiple myeloma is sparse and indirect.

#### *Acute Myelogenous Leukemia in the Children of Veterans*

Three studies have pointed to an association between paternal Agent Orange exposure and acute myeloid leukemia (AML) in children. The first was a case-control study of 204 children with AML, reported by the Children's Cancer Study Group, a US-Canada consortium.<sup>74</sup> The odds ratio associated with paternal long-term occupational pesticide exposure was 2.7 (95% CI, 1.0-7.0). As for maternal exposure, seven case mothers and no control mothers reported such exposure. The risk was elevated for children diagnosed before the age of six and for children who had sustained direct pesticide exposure. "Pesticides" in this study included both insecticides and herbicides, so it is not clear which agents were associated with the increased risk.

The second study was a survey of nearly 50,000 Australian Vietnam veterans.<sup>32</sup> This study also found an increase in AML among the children of Vietnam veterans, with a relative risk of 4.3. The risk of acute lymphocytic leukemia (ALL) was not increased in this study.

The third study, a case-control study of 1,805 cases of ALL and 528 cases of AML, was also reported from the Children's Cancer Group.<sup>75</sup> Although military service in general conferred no increased risk of childhood leukemia, service in Vietnam or Cambodia was associated with an odds ratio of 1.7 for AML (and no increased risk of ALL). Self-reported exposure to Agent Orange was not associated with increased risk.

#### *Gastrointestinal (GI) Cancer*

Cancers of the esophagus, stomach, pancreas, colon, and rectum have been extensively studied in Vietnam veterans, occupational groups with herbicide exposure, and people exposed to dioxins. These studies have yielded a fairly consistent pattern of no association between these exposures and any GI cancer.<sup>12</sup> One case-control study in Hanoi suggested that former military service, presumably entailing Agent Orange exposure, was associated with increased risk of hepatocellular carcinoma, but the risk was far smaller than that associated with Hepatitis B infection.<sup>76</sup>

#### *Brain Cancer*

Similarly, there is a fairly consistent pattern suggesting no association between Vietnam service, occupational herbicide exposure, or dioxin exposure, and brain cancer.<sup>12</sup>

#### *Other Cancers*

Available evidence does not permit a conclusion regarding an association between Agent Orange exposure and other cancers, including cancers of the nose and nasopharynx, breast, cervix, uterine corpus, ovaries, liver and biliary tree, bone, kidneys, urinary bladder, testicles, or skin, or leukemia (in veterans themselves, as opposed to their offspring).<sup>12</sup>

#### **Animal and Laboratory Studies**

The chlorophenoxyacetic acid herbicides such as 2,4,5-T and 2,4-D are not considered highly toxic compounds, and high doses are required to cause adverse effects in animals. These compounds have not been associated with cancer in animal bioassays. In vitro laboratory cancer bioassays have also generally been negative, although 2,4-D induced mutations in one bioassay.<sup>12</sup>

Cacodylic acid is reported to cause lung and bladder tumors, to promote skin cancer in mice, and to be mutagenic in some laboratory tests.<sup>77</sup> Picloram has caused increases in benign liver tumors and in thyroid adenomas in rats, but has not been mutagenic in vitro.<sup>78</sup>

2,3,7,8-TCDD is carcinogenic in animal tests, increasing in a wide variety of tumors in rats, mice, and hamsters. This action is thought to be mediated by the aryl hydrocarbon receptor (AhR), which triggers cellular signaling, DNA binding, and transcriptional activation. In vitro, TCDD does not seem to act as a direct genotoxin but has tumor-promoting activity instead.<sup>79</sup>

#### **What Expert Agencies Say**

Public Law 102-4, the "Agent Orange Act of 1991," directed the Secretary of Veterans Affairs to request the National Academy of Sciences to review and evaluate the effects of Agent Orange exposure. The Institute of Medicine, part of the National Academy of Sciences, responded by forming the Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides. The Committee has issued a series of studies, beginning with its 1994 *Veterans and Agent Orange: Health Effects of Herbicides Used in Vietnam*. The IOM reports have assessed the risk of both cancer and non-cancer health effects. Each health effect is categorized as having "sufficient evidence of an association," "limited/suggestive evidence of an association," "inadequate/insufficient evidence to determine whether an association exists," or "limited/suggestive evidence of no association." This framework provides a basis for policy decisions in the face of uncertainty.<sup>80</sup> As

TABLE 1

Associations Between Agent Orange Exposure and Cancer	
Sufficient evidence of an association	<ul style="list-style-type: none"> <li>● Soft-tissue sarcoma</li> <li>● Non-Hodgkin lymphoma</li> <li>● Hodgkin disease</li> <li>● Chronic lymphocytic leukemia (CLL)</li> </ul>
Limited/suggestive evidence of an association	<ul style="list-style-type: none"> <li>● Respiratory cancers (lung, trachea/bronchus, larynx)</li> <li>● Prostate cancer</li> <li>● Multiple myeloma</li> </ul>
Inadequate/insufficient evidence to determine whether an association exists	<ul style="list-style-type: none"> <li>● Hepatobiliary cancers</li> <li>● Nasal/nasopharyngeal cancer</li> <li>● Bone cancer</li> <li>● Breast cancer</li> <li>● Female reproductive cancers (cervical, uterine, ovarian)</li> <li>● Urinary bladder cancer</li> <li>● Renal cancer</li> <li>● Testicular cancer</li> <li>● Leukemia (other than CLL)</li> <li>● Skin cancers</li> <li>● Acute myelogenous leukemia in the children of veterans</li> </ul>
Limited/suggestive evidence of <b>no</b> association	<ul style="list-style-type: none"> <li>● Gastrointestinal cancers (stomach, pancreas, colon, rectum)</li> <li>● Brain tumors</li> </ul>

of the most recent update,<sup>12</sup> the associations between Agent Orange exposure and cancer were designated as shown in Table 1. (Note that other diseases, such as chloracne and diabetes, show evidence of an association, but this table shows only the cancers.)

The National Toxicology Program evaluates exposures that may be carcinogenic. Exposures that are thought to be carcinogenic are included in the Reports on Carcinogens, published every two years. Each exposure is assigned to one of two categories: "known to be human carcinogens," and "reasonably anticipated to be human carcinogens." The first category includes substances for which human studies (epidemiology studies and/or experimental studies) provide "sufficient evidence" of carcinogenicity in humans. The second category includes substances for which there is limited evidence of carcinogenicity in humans and/or sufficient evidence of carcinogenicity in experimental animals. The National Toxicology Program has not listed the chlorophenoxy herbicides, including Agent Orange, as carcinogens, but 2,3,7,8-TCDD is classified as "known to be a human carcinogen."<sup>81</sup>

The International Agency for Research on Cancer (IARC) also evaluates exposures that

may be carcinogenic. IARC classifies exposures in one of four categories: Group 1 exposures are those "known to be carcinogenic to humans," usually based on "sufficient" human evidence, but sometimes based on "sufficient" evidence in experimental animals and "strong" human evidence. Group 2 exposures are divided into two categories. Group 2A ("probably carcinogenic to humans") has stronger evidence, and Group 2B ("possibly carcinogenic to humans") has weaker evidence. Group 3 exposures are not considered classifiable, because available evidence is limited or inadequate. Finally, Group 4 exposures are "probably not carcinogenic to humans" based on evidence suggesting lack of carcinogenicity in humans and in experimental animals. IARC has not rated Agent Orange per se, but the chlorophenoxy herbicides, including 2,4-D and 2,4,5-T, are categorized as "possibly carcinogenic to humans" (Group 2B),<sup>82</sup> and 2,3,7,8-tetrachlorodibenzo-para-dioxin is categorized as "known to be carcinogenic to humans" (Group 1).<sup>79</sup>

The Environmental Protection Agency (EPA), through its Integrated Risk Information System, uses a classification scheme very similar to that of IARC. It classifies exposures into one

of five categories: (1) human carcinogen, (2) probable human carcinogen, (3) possible human carcinogen, (4) not classifiable as to human carcinogenicity, and (5) evidence of noncarcinogenicity for humans. EPA has not classified either phenoxyacetic acids or TCDD as to carcinogenicity.

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#### ASSOCIATION WITH OTHER HEALTH PROBLEMS

Vietnam service and Agent Orange exposure in particular have been extensively studied in relation to health problems other than cancer. High levels of dioxin exposure are associated with chloracne, a distinctive form of acne. Dioxin exposures are also associated with porphyria cutanea tarda, although this disorder has not been found in excess in Vietnam veterans. For other health effects, the evidence is more variable.<sup>12</sup>

There has been considerable concern about reproductive effects, such as birth defects in the children of exposed veterans. Some data are suggestive, especially with regard to neural tube defects, but this is an area that continues to be marked by great uncertainty. There has also been concern about neurotoxicity, including neuropsychiatric dysfunction, deficits in motor function, and peripheral neuropathy. Again, considerable uncertainty exists about these associations. Although the immune system is a target of dioxin, available evidence to date has not demonstrated an increase in immune disorders in veterans. Some evidence exists of an association between Agent Orange exposure and diabetes.<sup>10</sup> For other disorders—asthma, GI disease, circulatory disorders, and others—there is little definitive evidence of an association with Agent Orange.

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#### ADVISING PATIENTS

A Vietnam veteran with Agent Orange exposure may be eligible for three kinds of benefits.<sup>83</sup> Clinicians who are familiar with these benefits can counsel their patients who are veterans accordingly.

The first benefit is the Agent Orange Registry, a health examination program administered by the VA since 1978. Veterans who participate in this program receive medical examinations, basic laboratory evaluations, and specialty referrals if appropriate.

The second benefit is disability compensation payments. Such payments are available to veterans with service-related illnesses or illnesses that were incurred or aggravated by military service. The amount of the payments is determined by the extent of disability. Because past Agent Orange exposure is difficult to quantify, the VA uses a presumption-based system. 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. 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, or trachea occurring within 30 years of exposure to Agent Orange, soft tissue sarcoma (other than osteosarcoma, chondrosarcoma, Kaposi sarcoma, or mesothelioma), and chronic lymphocytic leukemia. The rationale for the 30-year limit on compensability for respiratory cancers is not clear. (Conditions other than cancer, such as diabetes, are also on this list.)

Third, some veterans qualify for medical care following Agent Orange exposure. According to the Veterans' Health Care Eligibility Reform Act of 1996, Public Law 104-262, the VA must provide its Medical Benefits Package—including outpatient and inpatient medical care at VA facilities, prescription medications, and home health and hospice care—to veterans with disorders associated with herbicide exposure in Vietnam (to the extent that Congress appropriates funds to provide this care). These disorders include the cancers presumed to be Agent Orange-related, as well as any other disorder that a VA physician determines is possibly associated with Agent Orange exposure during service in Vietnam. Under this

law, two categories of disability are excluded from care: a disability that the VA determines did not result from Agent Orange exposures (such as appendicitis or an injury from an automobile crash) or a disease that the National Academy of Sciences classifies as having limited/suggestive evidence of no association with Agent Orange (GI tumors and brain tumors).

Veterans may be referred to the VA Web site (<http://www.vba.va.gov/bln/21/benefits/herbicide/>) or to their local VA hospitals for further information on any of these Agent Orange-related benefits.

Clinicians can also provide clinical advice and careful routine medical care to patients with a history of Agent Orange exposure. Because of the possibility of excess cancer risk, patients should be advised to seek recommended cancer screening tests and should promptly seek medical evaluation of suspicious symptoms. Patients should also be advised to quit smoking, to avoid exposures to other carcinogens, to eat a diet primarily from plant sources, and to maintain a healthy body weight.

A veteran concerned about past occupational exposure to Agent Orange may want to join a support group at the local VA hospital and/or consult an occupational and environ-

mental medicine clinic. These clinics can help assess past exposures and any risk that may persist and recommend appropriate steps to health protection. They may be located through the Association of Occupational and Environmental Clinics at [www.aoec.org](http://www.aoec.org).

#### FOR FURTHER INFORMATION

For medical information, the definitive source is the series of IOM reports, *Veterans and Agent Orange*. These can be found at the National Academies Press Web site. The most recent update is available at: <http://bob.nap.edu/books/0309086167/html/>.

Several web sites are devoted to Agent Orange, including both government sites and private sites. The Department of Veterans Affairs maintains a site at <http://www.va.gov/agentorange/> in addition to the benefits site noted above. A useful brochure found there is "Agent Orange: Information for Veterans Who Served in Vietnam." (see [http://www.va.gov/agentorange/docs/IDAO\\_Brochure.PDF](http://www.va.gov/agentorange/docs/IDAO_Brochure.PDF)). The New Jersey Agent Orange Commission is at <http://njaoc.org/>. A private publishing company, Lewis Publishing, maintains a Web site at <http://www.lewispublishing.com/orange.htm>.

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