

Birth Defects Caused by Agent Orange ^[1]

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During the Vietnamese War between 1961 and 1971 the United States armed forces engaged in a defoliation and crop destruction campaign named Operation Ranch Hand. Agent Orange, an herbicide so named because of the orange color of its storage barrels, was the most heavily used herbicide of the campaign. In addition to military personnel from Australia, New Zealand, South Korea, North Vietnam, South Vietnam, and the United States, an estimated 4.8 million Vietnamese were exposed to herbicides during the war. In the years following the war reports of increased rates of [birth defects](#) ^[3] in the offspring of United States military personnel, Vietnamese soldiers, and civilians prompted several studies to explore the connection between Agent Orange exposure and [birth defects](#) ^[3]. Studies performed over three decades by the United States Centers for Disease Control and Prevention (CDC), the Australian government, and by Vietnamese researchers obtained mixed results. Several of these studies found, among the offspring of parents exposed to Agent Orange, higher than normal rates of [neural tube](#) ^[4] [birth defects](#) ^[3] such as [spina bifida](#) ^[5] and anencephaly. However, despite large sample sizes in many of these studies, the inherently low incidence of [birth defects](#) ^[3] resulted in weak statistical correlations with Agent Orange exposure. Furthermore, the publication of statistically significant, yet potentially biased findings by Vietnamese research agencies linking Agent Orange exposure and [birth defects](#) ^[3] has fueled global scientific debate about the issue.

In the 1940s, Arthur W. Galston, a graduate student in botany at the [University of Illinois](#) ^[6] in Urbana-Champaign, Illinois, discovered that a particular synthetic chemical, if applied in low enough concentrations, could speed up the flowering of plants. Conversely, high concentrations caused the leaves of plants to fall off, killing the plants. Based on Galston's thesis, military researchers devised a powerful herbicide to defoliate forests during the Vietnam War: Agent Orange. Beginning in 1961 the United States military used the herbicide, largely produced by the Monsanto Corporation in Missouri and Dow Chemical in Michigan, to destroy dense jungle to gain a tactical advantage over the North Vietnam guerillas, the Viet Cong. As the war persisted, increasing amounts of the chemical were used and expanded to target Vietnamese agricultural products. The stated purpose of such tactics was to starve the entrenched Viet Cong fighters, and to provoke civilians to relocate into US controlled cities. Until 1971 the United States government reported treating an estimated 2.6 million hectares in South Vietnam with pesticides during Operation Ranch Hand, approximately twelve percent of the area of the country. Agent Orange, among other colorfully named herbicidal chemicals such as Agent Blue, were dispersed aurally, by boat, and by ground forces.

Agent Orange released during Operation Ranch Hand contained 2,3,7,8-tetrachlorodibenzodioxin (TCDD), a dioxin which is linked to increase rates of cancer and [birth defects](#) ^[3]. Dioxin is fat soluble and enters the body through physical contact, inhalation, or ingestion of contaminated food or water. As it is fat soluble, this toxin accumulates in organisms as it moves up the food chain, and carnivores will have higher amounts stored in their bodies than herbivores or plants. When a pregnant mother is exposed to dioxin, the

teratogen can enter the embryo via the bloodstream. Dioxin is taken up by the body by attaching to a protein called the aryl hydrocarbon receptor (AhR), a transcription factor. The inactive AhR protein is located in the cytoplasm of most cells, and contains a receptor that is capable of interacting with several kinds of ligands. When dioxin binds to AhR, the protein moves to the [nucleus](#) [7], where it influences gene expression. In normal development gene expression timing and levels are tightly controlled; changing those things can result in [birth defects](#) [3].

In the years following the Vietnam War reports, of high rates of miscarriages, premature births, congenital [birth defects](#) [3], and infant mortality began to surface from regions in Vietnam where Agent Orange was used. In 1984, the CDC showed that the offspring of male veterans exposed to herbicides during the Vietnam War had increased rates of [neural tube](#) [4] defects, especially [spina bifida](#) [5], and to a lesser degree anencephaly. The study suggested that the dioxin present in Agent Orange caused [neural tube](#) [4] defects in offspring by either mutating a gene or chromosome on the [sperm](#) [8] before [fertilization](#) [9], or the dioxin was transmitted with the [sperm](#) [8].

The CDC's study focused on children born in the Atlanta area between the years of 1968 and 1980. The study contained two cohorts of children, those born to veterans, and those born to non-veterans. Parents in both groups were interviewed, and medical records of the children in the study were examined. In the group of children born to veterans, Agent Orange exposure was determined by the area of military assignment and occupation of the father during the Vietnam War. The study showed that those men who had reported a higher exposure to Agent Orange had a higher than normal likelihood of fathering children with [spina bifida](#) [5].

In 1988, the CDC performed a congress-mandated study on the health of Vietnam War veterans titled the "Vietnam Experience Study." The third part of this study compared two cohorts of veterans, those who had served in Vietnam, and those who had served in the armed services during the Vietnam War, but not in Vietnam. The structure of the study was similar to the 1984 study; those in both groups were interviewed and their medical records were examined. The results of the study showed a higher incidence of [spina bifida](#) [5], anencephaly, and [hydrocephalus](#) [10] in children of Vietnam veterans, especially those whose parents had been involved in what were called defoliating missions using Agent Orange. However, while the incidence among the offspring of Vietnam veterans was significantly higher than the control group of other veterans, the overall rate was consistent with birth defect rates reported in the general population. The tentative connection between exposure to defoliators such as Agent Orange and [birth defects](#) [3] led to a call for additional studies.

A 1995 study by William Wolfe and colleagues, based out of the Armstrong Laboratory on Brooks Air Force Base in San Antonio, Texas, attempted to clarify the connection between [birth defects](#) [3] and Agent Orange exposure. During this study, researchers collected the medical records of children of veteran's of the Vietnam War, and they interviewed their parents. Researchers reported increased rates of [neural tube](#) [4] defects in the children of exposed veterans. However, due to the low number of children in the study with [neural tube](#) [4] defects, five, researchers were unable to conduct appropriate statistical analysis to indicate an association between dioxin exposure and the increase in [birth defects](#) [3]. The report stated that the inherently low rates of certain [birth defects](#) [3] made determining statistical significance an unlikely outcome, and it concluded that there was little to no evidence for a statistical link between Agent Orange exposure and [birth defects](#) [3].

In 1991, in response to pressures from the Office of Veteran's Affairs and its allies, the United States Government passed the Agent Orange Act. This act mandates the US government to pay for the medical care of any Vietnam War veteran, regardless of length of service, related to an Agent Orange disease. These recognized diseases include several types of cancer, Parkinson's disease, and ischemic heart disease. In addition, The US congress passed subsequent bills to include compensation for children with [spina bifida](#) [5] and other [birth defects](#) [3] born to female veterans.

Researchers have struggled to describe the effects of Agent Orange on Vietnamese civilians and for several reasons. First, the effect of dioxin on embryonic development varies by the amount of dioxin the embryo is exposed to. Many of those who researched Vietnamese populations studied medical records and self reports of exposure, thus quantitative measures of exposure were rare. Second, dioxin persists in soil, which can contaminate future crop yields. Dioxin can also contaminate [fish](#) [11], a major food source in Vietnam, one hypothesized to be the major source of dioxin exposure to Vietnamese civilians. Because dioxin can persist in the environment, researchers struggle to estimate dioxin exposure levels and to definitively state the source of that dioxin exposure.

In 2006 Anh Duc Ngo, based out of the University of Texas Health Science Center in Austin, Texas, and his colleagues conducted a meta-analysis of studies investigating Agent Orange exposure and [birth defects](#) [3]. The analysis included nine publications predominantly from the United States, and the thirteen from Vietnamese sources. This sample of publications was reportedly selected to analyze and eliminate methodological flaws, to account for differences in exposure levels across cohorts in international studies, and to account for the large amount of data largely ignored in Western studies that involved Vietnamese civilians and language biases. However, eleven of the Vietnamese sources and two of the US sources were from unpublished, non-peered reviewed studies, which confounded the study's conclusions for many. The study reported a large amount of heterogeneity between studies, a finding consistent with the lack of scientific consensus on the issue. Despite that result, the meta-analysis concluded a causal relationship between Agent Orange exposure and stillbirth, cleft palate, and [neural tube](#) [4] defects. Consistent with previous studies, incidence of [spina bifida](#) [5] was the most statistically significant defect linked to Agent Orange exposure. Duc Ngo and his colleagues noted that most Vietnamese studies had methodological weaknesses and little validation of findings. To address those problems, Duc Ngo and colleagues also conducted analysis only including non-Vietnamese publications. While the statistical significance of the relationship between herbicide exposure and [birth defects](#) [3] fell, the links were still statistically significant.

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Subject

Agent Orange [13] Vietnam War, 1961-1975 [14] Agent Orange [13] Tetrachlorodibenzodioxin [15] Fetal development

[\[16\] Birth defects](#) [\[17\] Fetus](#) [\[18\] Fetus--Abnormalities](#) [\[19\] Pregnancy](#) [\[20\] Teratology](#) [\[21\] Embryos](#) [\[22\] Neural tube--Abnormalities](#) [\[23\] Spina bifida](#) [\[24\] Hydrocephalus in infants](#) [\[25\] Congenital, Hereditary, and Neonatal Diseases and Abnormalities--Congenital Abnormalities](#) [\[26\]](#)

Topic

[Disorders](#) [\[27\]](#) [Reproduction](#) [\[28\]](#)

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- [2] <https://embryo.asu.edu/keywords/birth-and-developmental-defects>
- [3] <https://embryo.asu.edu/search?text=birth%20defects>
- [4] <https://embryo.asu.edu/search?text=neural%20tube>
- [5] <https://embryo.asu.edu/search?text=spina%20bifida>
- [6] <https://embryo.asu.edu/search?text=University%20of%20Illinois>
- [7] <https://embryo.asu.edu/search?text=nucleus>
- [8] <https://embryo.asu.edu/search?text=sperm>
- [9] <https://embryo.asu.edu/search?text=fertilization>
- [10] <https://embryo.asu.edu/search?text=hydrocephalus>
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