

Agent Orange as a Cause of Spina Bifida

Spina bifida is a birth defect that affects the spines of developing fetuses and infants, and research in the 20th century indicated that chemicals in the herbicide Agent Orange likely led to the birth defect. People with spina bifida can have nerve damage, paralysis, and mental disabilities. During the Vietnam War in the 1960s, the US military employed Agent Orange and other herbicides to destroy enemy crops and forest cover until 1970. Though studies of the link between Agent Orange exposure and birth defects were at first inconclusive, in 1995 the US National Academy of Sciences concluded that one birth defect, spina bifida, was associated with paternal Agent Orange exposure. Spina bifida was, by the twenty-first century, the only birth defect that the US Veterans Administration connected to Agent Orange exposure.

Spina bifida, from the Latin for split spine, is a condition in which the neural tube of a fetus fails to develop normally into a brain, spinal cord, and enveloping tissues. The incomplete development leads to an opening or malformation in the spine, which, depending on the location, the size, and the exposure of the malformation, affects the severity of the condition.

In the most common form of spina bifida, called spina bifida occulta, the malformation is covered by a layer of skin. Because the spinal fluid and meninges, protective membranes around the spinal cord, are covered by skin, spina bifida occulta usually does not cause physical symptoms or disabilities. Doctors identified the condition by several physical factors above the spinal defect, including a small patch of hair, a small dimple, or birthmark.

A second form of spina bifida, called spina bifida meningocele, the opening of the spine may or may not be covered by a layer of skin. Whether the malformation is covered or not correlates with the severity of the physical symptoms, ranging from few or no symptoms to complete paralysis with bladder and bowel dysfunctions.

The third form of spina bifida, spina bifida myelomeningocele, occurs when the spinal defect is uncovered and the spinal fluid and spinal cord tissues are exposed. The resulting symptoms include nerve damage, loss of muscle function and muscle sensation, and partial or complete paralysis of the parts of the body below the spinal opening.

In both spina bifida meningocele and spina bifida myelomeningocele, the protruding meninges form a fluid-filled sac on the infant's back. Because the spinal nerves below the malformation are affected, defects that occur higher on the spinal cord tend to cause more severe symptoms. In addition to paralysis and reduced sensation, spina bifida can lead to the abnormal buildup of cerebrospinal fluid in the brain, a condition called hydrocephalus. If the excess fluid is not drained, the resulting pressure on the brain and spinal cord can damage the brain and affect mental development.

By the time of the Vietnam War in the 1960s and 1970s, studies had shown that many pharmaceutical drugs and chemicals were teratogens, a class of compound which adversely affects embryos and fetuses as they develop. In particular, studies found that pregnant women exposed to chemicals had a range of effects including spontaneous abortions, stillbirths, and newborns with birth defects.

During the Vietnam War, the US military used herbicides to combat the jungle-fighting tactics of enemy combatants in Vietnam. To clear the dense jungle foliage and eliminate potential enemy crops, US armed forces dispersed approximately nineteen million gallons of herbicides over Vietnam in a military campaign called Operation Ranch Hand. Code-named for the colored band on the steel containers, the herbicides included Agent Orange, Agent White, and Agent Pink. Of the defoliants, Agent Orange was the most extensively used and consisted of two compounds: 2,4-D (2,4-dichlorophenoxyacetic acid) and 2,4,5-T (2,4,5-trichlorophenoxyacetic acid).

Though the US government endorsed the safety of the herbicides, some of which were sold as commercial herbicides in the US, scientists from the US and abroad protested Operation Ranch Hand. They cited the potentially long-term consequences of spraying highly concentrated chemicals in a primarily agricultural society. The protests culminated in a mandate from the US Congress in 1965 to study the herbicides' toxicity, the results of which showed that 2,4,5-T, a compound in Agent Orange, contained a teratogenic contaminant related to stillbirths and birth defects in laboratory rats. The contaminant, TCDD (2,3,7,8-tetrachloro-dibenzo-para-dioxin), was a dioxin already known to produce adverse health effects. As early as 1949, workers at Monsanto Company's chemical plant in Nitro, West Virginia, had developed a skin disease called chloracne, after a chemical accident involving TCDD. Chloracne was one of the first documented health effects of TCDD exposure. Researchers later linked exposure to TCDD and other dioxins, in high doses, to cancers, skin diseases, and birth defects.

In the early 1970s, two separate committees of scientists, one non-governmental and one contracted by US Congress, traveled to Vietnam to assess the effects of the herbicides. Though their reports were inconclusive regarding the herbicides impact on human health, both contradicted earlier statements by the US government that the spraying of Agent Orange would not affect the Vietnamese civilian population. Rather, civilian food crops had been destroyed and local reports of stillbirths and birth defects increased. The US military suspended its use of Agent Orange in 1970, and discontinued Operation Ranch Hand in 1971.

Following the war, veterans from the US, Australia, and New Zealand reported birth defects in their children, in addition to their own adverse health outcomes. The second herbicide committee to travel to Vietnam, formed by the US National Academy of Sciences and by the US Congress, confirmed in 1974 that TCDD was extremely toxic to laboratory animals and linked to chloracne in humans. Their concerns culminated in a publicized class action lawsuit between an estimated 40,000 Vietnam veterans, their spouses, parents, and children, and the US chemical manufacturers of the herbicides used in the Vietnam War. After seven years, both sides reached a settlement in 1984 when seven chemical companies, including Dow Chemical Company in Midland, Michigan, and Monsanto Company, in St. Louis, Missouri, agreed to create a 180 million dollar fund for veterans and their families.

However, the 1984 settlement did not resolve the growing public concern that Agent Orange exposure had long-term effects on the children of veterans exposed to it. To address growing concerns and minimal scientific research on the potentially harmful effects of Agent Orange, the US government and US military conducted several studies on the health of Vietnam veterans in the 1980s.

In the 1984 Birth Defects Study, researchers from the Centers for Disease Control and Prevention (CDC) in Atlanta, Georgia, J. David Erickson and his research team assessed whether or not Vietnam veterans were at increased risk of fathering infants with birth defects. Using birth records taken from the metropolitan Atlanta area between 1968 and 1980, they studied two cohorts: a case group of infants with birth defects, and a control group of infants without birth defects. The researchers aimed to determine if there were more Vietnam veterans as fathers of the case group infants than in the control group. The researchers found approximately equal numbers of Vietnam veterans in the case group and the control group, leading them to conclude that overall, veterans were not at increased risk of fathering infants with birth defects.

In the second part of the study, the researchers estimated the amount of Agent Orange that veteran fathers had been exposed to via two methods, personal interview and military records. Erickson and his colleagues noted that veterans with higher exposure scores had a higher than normal risk of fathering infants with spina bifida. Though they described the finding as a statistical anomaly, the researchers stated that further attention should be given to the association between Agent Orange exposure and specific birth defects.

The second CDC study was the 1988 Vietnam Experience Study, in which the CDC assessed the physical health, psychological health, and reproductive health of Vietnam veterans. For each section, the CDC used military personnel records to compare the health of Vietnam veterans with non-Vietnam veterans who had served in the military during the same time period. Researchers Eugenia E. Calle, Muin J. Khoury, Linda A. Moyer, Coleen A. Boyle, M. Riduan Joesoef, and Robert

J. Delaney conducted interviews with both groups of veterans that included questions about the veterans' reproductive health, including, if any of their children had birth defects.

Calle and her colleagues noted that Vietnam veterans were more likely than non-Vietnam veterans to report birth defects in their children, though hospital birth records showed similar rates of birth defects between the two groups. Of the types of birth defects, the researchers found that Vietnam veterans reported higher rates of head and spine malformations, including spina bifida and hydrocephalus. However, an attempt to conduct a secondary study on cerebrospinal malformations failed, and the authors concluded that their findings were consistent with those of other studies—that Agent Orange could not be conclusively linked with the occurrence of birth defects.

Calle and her colleagues cited the ongoing efforts of a US Air Force Health Study, which surveyed the long-term health of veterans who handled and sprayed herbicides in the Vietnam War. After the initial US Air Force Health Study began in 1982, the US Air Force researchers conducted follow-up interviews and physical examinations on both veterans who had handled herbicides and veterans who had not handled herbicides. The physical examinations, which took place in 1982, 1985, 1987, and 1992, included laboratory testing, of blood, urine, and semen samples. In particular, the researchers measured the dioxin levels in the veterans to assess whether veterans with higher levels of dioxin also had adverse reproductive outcomes. Despite early evidence that there were more birth defects in the children of the Operation Ranch Hand veterans, the results had not yet been published in 1988, and therefore did not directly impact Calle and her colleagues' conclusions.

The CDC studies, the US Air Force Health Study, and a study the Australian government conducted on Australian Vietnam veterans, were the first major studies that focused on the association between birth defects of children with Vietnam service and Agent Orange exposure of parents. Though researchers in Vietnam also conducted studies on Vietnamese citizens and their children's birth defects, the research was unpublished and not peer reviewed. Erickson and his colleagues highlighted various methodological issues of Vietnamese studies, such as unverified data. Regarding their own studies, the research teams led by Erickson and Calle stated that methodological issues limited the CDC studies, such as the difficulty of measuring dioxin exposure and the complex factors that contribute to the occurrence of birth defects. Based on their inconclusive results, Erickson and his colleagues in the 1984 study recommended further investigation.

In 1991, US Congress enacted Public Law 102-4, also called the Agent Orange Act of 1991, whereby Congress acknowledged that Vietnam veterans with diseases shown to be caused by dioxin exposure could apply for disability compensation. Through the Act, Congress assumed several facts: that veterans with such diseases had been exposed to Agent Orange, and that the dioxin pollutants in Agent Orange were responsible for the veterans' diseases, which Congress termed service-connected diseases. Lastly, Congress directed the National Academy of Sciences to conduct reviews and evaluations of scientific literature every two years, to determine whether certain health problems were service-connected diseases and report those findings to the Veterans Administration. In the act, Congress listed the first service-connected diseases as chloracne, a skin disease, and two types of cancer, non-Hodgkin's lymphoma and soft-tissue sarcoma.

In 1996, the National Academy of Sciences published two reports, "Veterans and Agent Orange Update 1996" and "Veterans and Agent Orange Update 1996: Summary and Highlights," the latter of which highlighted the National Academy's new conclusion regarding spina bifida and Agent Orange. In the first 1994 report, the National Academy had concluded, based on the scientific literature published from the 1970s to 1994, that spina bifida was not linked to Agent Orange exposure. However, a 1995 update to the US Air Force Health Study led the committee to conclude that there was limited, suggestive evidence that Agent Orange exposure was associated with the occurrence of spina bifida in Vietnam veterans' children. In the study update in 1995, they noted that there were four neural tube defects in the Operation Ranch Hand group, compared with no neural tube defects among the comparison group's children.

When the National Academy of Sciences evaluated the 1995 results of the US Air Force Operation Ranch Hand study, along with the previous CDC studies from the 1980s, they changed their conclusion regarding the link between spina bifida and Agent Orange exposure. Due to the altered conclusions in the 1996 report, the Veterans Administration added spina bifida to the list of

service-connected diseases eligible for compensation. In 1996, the department began offering compensation to veterans whose children were born with severe forms of the condition: spina bifida meningocele and spina bifida myelomeningocele.

In 2006, researchers Anh Duc Ngo at the University of Texas in Houston, Texas, and collaborators from the University of Sydney in Sydney, Australia and the University of Queensland in Brisbane, Australia, published a literature review of twenty-two studies associating parental exposure to Agent Orange with birth defects. Ngo and his colleagues emphasized the significance of their literature review because they focused on unpublished Vietnamese studies that had not been reviewed by the National Academy of Sciences. According to the authors, they considered the Vietnamese studies a necessary part of the discussion that had not yet been included in previous investigations. The researchers concluded, based on thirteen Vietnamese studies and nine non-Vietnamese studies, that parental exposure to Agent Orange was linked with an increased risk of fathering children with birth defects. However, Ngo and his colleagues' paper was met with critical feedback that questioned the validity of the Vietnamese studies, due to the unpublished and inaccessible nature of the studies.

In 2010, Ngo and his colleagues released a second meta-analysis on the link between paternal exposure to Agent Orange and spina bifida, which partly addressed the criticism towards their first 2006 paper. In the second paper, they acknowledged that there were other causes of birth defects, besides Agent Orange, that may have affected their conclusions in the first study. Their purpose in the second literature review was to focus specifically on one birth defect, spina bifida, and its relation to on paternal Agent Orange exposure. Analyzing the combined results of seven studies involving three hundred thirty cases of spina bifida, Ngo and his colleagues concluded that paternal exposure to Agent Orange was associated with increased risk of spina bifida in the offspring. Of the seven studies, the five non-Vietnamese studies included the two aforementioned CDC studies, the Air Force Health Study, the Australian government study, and a more recent 2006 study by researchers at the University of Texas A&M in Houston, Texas.

In a 2016 paper on the risk factors of spina bifida, researchers from various Canadian institutions cited the 2010 meta-analysis by Ngo and his colleagues as strong evidence that paternal exposure to Agent Orange is a risk factor for spina bifida. While studies have not conclusively shown that dioxin exposure causes spina bifida, as of 2016, the US Department of Veterans Affairs considers spina bifida a service-connected disease and provides compensation to Vietnam veterans' children who have been diagnosed with spina bifida.

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