Agent Orange Birth Defects [1]

By: King, Jesse Chou, Cecilia Keywords: Agent Orange [2] Birth defects [3] Spina Bifida [4] Vietnam War [5]

Editor's Note: This article replaces the previous article on this topic, which was published in this encyclopedia in 2012. The 2012 article may be found at http://hdl.handle.net/10776/4202 [6].

Sprayed extensively by the US military in Vietnam, Agent Orange contained a dioxin contaminant later found to be toxic to humans [7]. Despite reports by Vietnamese citizens and Vietnam War veterans of increased rates of stillbirths and birth defects [8] in their children, studies in the 1980s showed conflicting evidence for an association between the two. In 1996, the US National Academy of Sciences [9] reported that there was evidence that suggested dioxin and Agent Orange exposure caused spina bifida [10], a birth defect in which the spinal cord develops improperly. The US Department of Veterans Affairs' subsequent provision of disability compensation for spina bifida-affected children marked the US government's first official acknowledgement of a link between Agent Orange and birth defects [8]. By 2017, spina bifida [10] and related neural tube [11] defects were the only birth defects [8] associated with Agent Orange.

Plant physiologists first developed herbicides as tools of chemical warfare toward the end of World War II. During the 1950s and 1960s, US researchers continued to develop means of chemical warfare at Fort Detrick in Detrick, Maryland. Their research built on the dissertation of Arthur W. Galston, a graduate student at the University of Illinois [12] in Urbana-Champaign, Illinois. Galston studied a particular synthetic chemical called 2,3,5-triiodobenzoic acid (TIBA), and he showed that in low concentrations TIBA quickened the flowering process of soybean plants. In high concentrations, however, the same compound caused the leaves to fall off, killing the plants. The military scientists at Fort Detrick used the results from Galston's dissertation to investigate other compounds that similarly defoliated and killed plants.

Agent Orange, the most extensively used herbicide in the Vietnam War, comprised an equal mixture of two such compounds: 2,4-D (2,4-dichlorophenoxyacetic acid) and 2,4,5-T (2,4,5-trichlorophenoxyacetic acid). The Monsanto Company in St. Louis, Missouri, and Dow Chemical in Midland, Michigan, produced most Agent Orange, which the US military sprayed throughout Vietnam to destroy dense jungle to gain a tactical advantage over the North Vietnamese guerillas, the Viet Cong. Agent Orange, named for the colored stripe on the steel containers, was used in conjunction with other herbicides like Agent Purple, Agent Blue, and Agent White in a military campaign called Operation Ranch Hand. Between 1962 and 1971, the US military dispersed roughly nineteen million gallons of herbicides over an estimated 3.6 million acres in South Vietnam. Approximately twelve million gallons of Agent Orange were sprayed, making it the most heavily used herbicide.

Scientists worldwide protested the military use of herbicides in Vietnam. Groups like the American Association for the Advancement of Science in Washington, D.C., warned against the potential long-term consequences of spraying herbicides in high concentrations on the landscape and civilians in Vietnam. As a result of scientists' lobbying efforts and the public's growing opposition to the war, the US government contracted Bionetics Laboratories in Yorktown, Virginia, in the mid-1960s to conduct a study on the toxicity of herbicides used in Vietnam. In the report, which was published in 1969, Bionetics researchers stated that Agent Orange contained a contaminant called 2,3,7,8-tetrachlorodibenzodioxin (TCDD), a dioxin that caused increased rates of stillbirths and birth defects [8] in pregnant rats exposed to it. In 1970, the US Surgeon General's office reported that 2,4,5-T, the component of Agent Orange that contained the TCDD contaminant, may be hazardous to human health.

Dioxins, including TCDD, are a group of compounds considered to be persistent organic pollutants, or organic compounds that remain intact in the environment for long periods of time. While people generally encounter dioxins when they unintentionally ingest them, exposure can also occur through physical contact or inhalation. As fat-soluble compounds, dioxins accumulate in the fatty tissues of organisms, meaning that carnivores with more fatty tissues have higher amounts stored in their bodies than herbivores or plants. In the tissues, dioxins attach to a protein receptor called the aryl hydrocarbon receptor, which is hypothesized to act like a switch that affects many developmental processes including embryo development and normal growth. Some researchers hypothesized that the activated aryl hydrocarbon receptor leads to a toxic response by the body, which can cause problems in developing embryos and fetuses.

Following the discovery of dioxin in Agent Orange in 1969, several scientific groups attempted to determine the effects of Agent Orange in Vietnam. In 1970, a committee from the American Association for the Advancement of Science traveled to Vietnam to assess the effects of herbicides sprayed during the Vietnam War. In addition to studying how the environment was affected by the herbicides, the committee noted that local reports of stillbirths and birth defects [8] might be linked to the dioxin contaminant in Agent Orange. In 1974, a second committee that traveled to Vietnam, formed by the National Academy of Sciences [9] and by the US Congress, confirmed that the dioxin contaminant, TCDD, in Agent Orange was extremely toxic to laboratory animals and caused chloracne, an inflammatory skin disease, in humans [7].

The reports by both committees coincided with studies by Vietnamese scientists and Vietnamese citizens in Agent Orange spray zones which reported high rates of miscarriages, premature births, congenital birth defects [8], and infant mortality in those areas. Returning US veterans also reported increased rates of birth defects [8] in their children, leading many veterans and the public to wonder whether Agent Orange exposure had negative health effects. As a result, in the 1980s, scientists in the US, Australia, and Vietnam began to study the effects of exposure to Agent Orange in Vietnam veterans.

Two studies conducted by the Centers for Disease Control (CDC) in Atlanta, Georgia, investigated whether Agent Orange exposure was linked to birth defects [8]: the 1983 Birth Defects Study and the 1988 Vietnam Experience Study. In the 1983 Birth Defects Study, CDC researchers studied if Vietnam veterans were more likely to father children with birth defects [8]. The researchers studied two cohorts of

children born in the metropolitan Atlanta area between 1968 and 1980, one with birth defects [8] and the other without. They determined that in each group, the percentage of fathers who had served in Vietnam was approximately nine percent, suggesting that veterans were not at increased risk of fathering infants with birth defects [8]. The researchers also attempted to measure Agent Orange exposure of the male veterans through military records and interviews, finding that veterans with more exposure reported more birth defects [8] in their offspring. However, the CDC researchers stated that their study was not sufficient to determine a link between Agent Orange exposure and the occurrence of those birth defects [8].

In the 1988 Vietnam Experience study, CDC researchers compared the health of Vietnam War veterans with veterans who had served during the Vietnam War period, but not in Vietnam. A portion of the study focused on the reproductive health of the Vietnam veterans, specifically whether or not the veterans had children with birth defects. CDC researchers interviewed two groups of Vietnam and non-Vietnam veterans and examined their medical records. Though the researchers found that Vietnam veterans reported more birth defects [8] in their children than did non-Vietnam veterans, the medical records showed that the rates of birth defects [8] were nevertheless similar between the two groups of veterans. Therefore, the researchers reported that their findings were consistent with the results of the 1983 CDC study and that Vietnam veterans were not at increased risk of fathering children with birth defects [8].

In both studies, CDC researchers found that among the wide range of birth defects [8] reported by Vietnam veterans, more veterans reported a specific birth defect, spina bifida [10], and other birth defects related to the head and spine (cerebrospinal). Despite some evidence that more Vietnam veterans than non-Vietnam veterans fathered children with cerebrospinal malformations, the CDC researchers in the 1988 study made similar conclusions as the 1984 study. The authors stated that further research was needed to ascertain whether certain birth defects [8] were caused by Agent Orange exposure.

Other research groups aside from the CDC also studied whether or not Vietnam veterans' exposure to Agent Orange caused birth defects [8] in their children. One such study was the US Air Force's ongoing health study on veterans who handled and sprayed herbicides in the Vietnam War. After 1982, Air Force researchers interviewed and physically examined veterans, comparing their results with Air Force veterans who had not handled herbicides. Despite early evidence that there were more birth defects [8] in the Vietnam veterans group, no conclusions had been published by the time of the CDC's Vietnam Experience Study in 1988. As such, the preliminary results from the Air Force Health Study were not used as evidence of Agent Orange's effect on birth defects [8].

In 1990, researchers Ann Aschengrau and Richard R. Monson conducted another study that investigated the impact of paternal military service in Vietnam on the prevalence of birth defects [8] in the children of patients at the Boston Hospital for Women in Boston, Massachusetts. As with the previous CDC and Air Force studies, Aschengrau and Monson conducted a case-control study, for which they compared two groups: a case group of infants with congenital malformations, and a control group of infants without any malformations. In both groups, the researchers categorized the fathers of the infants as Vietnam veterans, non-Vietnam veterans, or civilians, and then they assessed whether or not there were more congenital anomalies in one of the three groups.

Although Aschengrau and Monson found that overall Vietnam veterans were at slightly higher risk of fathering infants with certain congenital malformations, they noted two limitations to their findings. First, the authors considered the sample group of subjects to be too small, especially when comparing specific birth defects. Second, they noted that the congenital anomalies could also be related to maternal behaviors during the pregnancy [13] and complications during delivery, not just paternal exposure to Agent Orange. Like the CDC researchers, Aschengrau and Monson recommended larger studies to clarify whether or not Vietnam veterans or Agent Orange-exposed Vietnam veterans were at increased risk of adverse pregnancy [13] outcomes like birth defects [8] and stillbirths.

In 1991, US Congress enacted the Agent Orange Act of 1991. Through the Act, Congress directed the National Academy of Sciences [9] to regularly review scientific literature regarding Agent Orange's health effects and to compile a list of Agent Orange-related diseases for the Department of Veterans Affairs, headquartered in Washington, D.C. The Act then mandated Veterans Affairs to compensate veterans with Agent Orange-related diseases, diseases caused by dioxin exposure that Congress termed service-connected diseases. In 1991, the only established service-connected diseases were two kinds of cancers, non-Hodgkin's lymphoma and soft-tissue sarcoma, and a skin disease called chloracne.

In 1996, Veterans Affairs acknowledged an association between Agent Orange exposure and birth defects [8] when they added the spina bifida to the list of service-connected diseases. The addition of spina bifida [10] followed the publication of the update to the 1982 Air Force Health Study that compared health outcomes of both veterans who handled and sprayed Agent Orange and veterans who did not. After a follow-up examination in 1992, the Air Force researchers found four cases of neural tube [11] birth defects [8] in the children of the Vietnam veterans compared to zero cases in the children of the non-Vietnam veterans. However, the researchers stated that the inherently low rates of certain birth defects [8] made determining statistical significance difficult, and concluded that there was still little to no evidence for a statistical link between Agent Orange exposure and birth defects [8].

Despite the conclusion of the US Air Force researchers, the National Academy of Sciences [9] Institute of Medicine committee considered the Air Force update, in conjunction with the CDC studies and the Boston Hospital study, as evidence that dioxin exposure through Agent Orange may be linked to neural tube [11] defects. The most common neural tube [11] defects, which are birth defects [8] of the brain, spine, and spinal cord, are spina bifida [10] and anencephaly. Whereas spina bifida [10] occurs when the spinal cord and enveloping tissues do not develop properly, anencephaly occurs when the brain and skull do not develop properly. Following the committee's 1996 report, Veterans Affairs began offering compensation for veterans' children with spina bifida [10]. However, the studies that the Institute of Medicine committee considered, including the US Air Force Health Study, the CDC studies, and several others, still did not lead the committee to conclude that Agent Orange caused other birth defects [8] besides spina bifida [10].

Several factors affected the committee's conclusion not to acknowledge a link between Agent Orange exposure and birth defects [8] besides spina bifida [10]. For example, maternal exposure to chemicals as well as substances like tobacco and alcohol greatly affect prenatal development. However, such exposure was not evaluated in the studies. In the Vietnam veterans' health studies, the researchers focused

primarily on the health outcomes of the male veterans. And while epidemiologic studies and historical events showed the link between maternal behaviors, maternal exposures, and birth defects [8], the CDC researchers acknowledged that the paternal association to birth defects [8] was less understood. Additionally, they noted that the results likely were biased due to the difficulty of measuring dioxin exposure and to the reliance on veterans' or citizens' self-reported exposure. Finally, because certain commercial herbicides contained dioxins and dioxins persist in the soil and the environment, researchers struggled to estimate dioxin exposure levels and to identify the source of that dioxin exposure. For those reasons, the Institute of Medicine committee added only spina bifida [10] to the list of service-connected diseases that received compensation from the Department of Veterans Affairs.

Han Kang, an epidemiologist for Veterans Affairs, attempted to link birth defects [8] in the children of female Vietnam military service. In 2000, without attempting to find a cause for specific pregnancy [13] outcomes, Kang and his colleagues used health questionnaires, military records, and interviews, to record the negative pregnancy [13] outcomes of female veterans of the Vietnam War, including stillbirth, spontaneous abortion [14], low birth weight, and birth defects [8]. In their comparison of approximately four thousand female Vietnam veterans and non-Vietnam veterans, the researchers found that the Vietnam veterans experienced a higher prevalence of birth defects [8] among their children.

Despite acknowledging methodological issues including incomplete medical records, reliance on self-reporting, and a thirty-year gap between the war period and the data collection, Kang and his colleagues concluded that Vietnam service was linked to increased rates of birth defects [8], including spina bifida [10] and anencephaly. Soon after, US Congress enacted Public Law 106-419 in 2000, which authorized Veterans Affairs to offer compensation for female Vietnam veterans whose children had specific birth defects [8]. Through the law, Congress recognized links between birth defects [8] and Vietnam military service by female veterans, but not to the exposure of these women to herbicides like Agent Orange.

In 2006, researcher Anh Duc Ngo and his colleagues at the University of Texas Health Science Center in Austin, Texas, conducted a literature review of studies that had investigated Agent Orange exposure and birth defects [8]. Ngo and his colleagues examined unpublished studies from researchers in Vietnam that the National Academy of Sciences had not considered in their regular reports to the Department of Veterans Affairs. Ngo's team aimed to address the inconclusive research about the health effects of Agent Orange. The analysis included thirteen studies from Vietnam, eleven of which were unpublished, and nine studies from the US and Australia. While noting the methodological weaknesses of the Vietnamese studies, the Ngo and his colleagues argued for a causal relationship between Agent Orange exposure and the risk of birth defects [8], with a stronger association existing in Vietnamese populations than in non-Vietnamese populations.

The review by Ngo and his colleagues received criticism following its publication in 2006. Arnold Schecter at the University of Texas School of Public Health in Dallas, Texas, and physician John Constable from Harvard Medical School [15] in Boston, Massachusetts, stated that the association between Agent Orange and birth defects [8] was at most based on suggestive evidence. While commending Ngo and his colleagues' inclusive approach, Schecter and Constable noted that the unpublished, non-peer reviewed Vietnamese studies had relied heavily on self-reporting, often without verification through hospital records, meaning that the data were not reliable. While the Schechter and Constable stated their strong belief that Agent Orange had serious health effects, they highlighted a need for continuous, thorough research regarding the question of Agent Orange and other birth defects [8] other than neural tube [11] birth defects [8].

By 2016, spina bifida [10] was the only birth defect that the US government acknowledged as related to veteran exposure to Agent Orange, through paternal exposure to dioxins. Though Veterans Affairs compensated the families of veterans for specific birth defects related to maternal military service, studies had yet to establish a link between those birth defects [8] and paternal Agent Orange exposure.

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Subject

Agent Orange [37] Herbicide orange [38] Orange, Agent [39] Orange, Herbicide [40] Herbicides [41] Spina bifida [42] Neural tube--Abnormalities [43] Spinal cord--Abnormalities [44] Spine--Abnormalities [45] Spinal Dysraphism [46] Neural Tube Defects [47]

Topic

Disorders [48]

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[3] https://embryo.asu.edu/keywords/birth-defects
[4] https://embryo.asu.edu/keywords/spina-bifida
[5] https://embryo.asu.edu/keywords/vietnam-war
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