

## "Vietnam Veterans' Risks for Fathering Babies with Birth Defects" (1984), by J. David Erickson, Joseph Mulinare, Philip W. McClain, Terry G. Fitch, Levy M. James, Anne B. McClearn, Myron J. Adams, Jr.

In 1984, J. David Erickson and his research team published the results of a study titled "Vietnam Veterans' Risks for Fathering Babies with Birth Defects" that indicated that Vietnam veterans were at increased risk of fathering infants with serious congenital malformations, or birth defects. Researchers at the Centers for Disease Control (CDC) in Atlanta, Georgia, conducted the study to address the issue. Though the study's results were inconclusive, the study was one of the first to document a possible association between Vietnam War service and spina bifida, a lower back birth defect in which the spinal cord does not form properly. Later research established the links between Agent Orange exposure and various birth defects and led the US Department of Veterans Affairs to offer disability compensation for Vietnam veterans and their families who were affected by Agent Orange exposure.

During the Vietnam War, from 1961 to 1970, the US military sprayed approximately nineteen million gallons of herbicides over Vietnam as part of a defoliation and crop destruction campaign called Operation Ranch Hand. Protests from scientists and citizens over the possible health and ecological consequences of Operation Ranch Hand led to a government-mandated study in 1965 on the possible toxicity of the herbicides, and one herbicide in particular, Agent Orange. The study showed that Agent Orange contained a synthetic dioxin compound, 2,3,7,8-tetrachlorodibenzodioxin (TCDD), which caused fetal malformations and stillbirths in rodents exposed to TCDD while in utero. Following the study's results, the US military discontinued Operation Ranch Hand in 1971.

Before the war ended in 1975, civilians in Vietnam began to report an increased occurrence of birth abnormalities and stillbirths in areas that had been targeted by Agent Orange. Vietnam veterans from New Zealand, Australia, and the US made similar reports, and they reported a higher occurrence of specific cancers and skin diseases. In 1978, a group of US veterans further highlighted those consequences when they filed a lawsuit against the chemical manufacturers of the herbicides used in the Vietnam War.

The Centers for Disease Control subsequently began a study in 1982 to determine if Vietnam veterans were more likely to father infants with birth defects. The researchers who conducted the CDC study were J. David Erickson, Joseph Mulinare, Philip W. McClain, Terry G. Fitch, Levy M. James, Anne B. McClearn, and Myron J. Adams, Jr. Erickson was the Chief of the Birth Defects and Genetic Diseases Branch of the National Center for Environmental Health in Atlanta, Georgia, and the other authors were medical epidemiologists at the CDC. The team summarized the results in the *Journal of the American Medical Association* publication, and the CDC also released a comprehensive report on the study.

"Vietnam Veterans' Risks for Fathering Babies with Birth Defects" is a 10-page paper with a short introduction and 3 main sections: "Methods," "Results," and "Comment." The "Methods" section is further divided into 3 sections: "Selection of Cases and Controls," "Study Data," and "Analytic Approach." According to Erickson and his colleagues, to study the link between Agent Orange and the occurrence of birth defects, they measured the amount of Agent Orange to which the veterans had been exposed. The authors state that the best way to measure herbicide exposure was to question individual Vietnam veterans about their war experience and then to study the health outcomes of

their children. Although women were also exposed to Agent Orange in Vietnam, the study looked at predominantly men to study how paternal exposure to chemicals might be related to birth defects in children.

Erickson and his colleagues begin the introduction of the paper by explaining that the purpose of the study is to address Vietnam veteran concerns and to provide a brief overview of the use of Agent Orange in the Vietnam War. The authors state that certain chemicals are known to affect pregnant women, but that the link between paternal exposure to chemicals and birth defects is largely unknown. In the final part of the introduction, the authors reassert that their primary goal was not to focus on the link between Agent Orange and birth defects, but to determine if Vietnam veterans in general were at increased risk of fathering infants with birth defects.

The authors next begin the first main section, "Methods," starting with the subsection, "Selection of Cases and Controls." Erickson and his colleagues explain how they selected the case group, which consisted of infants with birth defects, and the control group, which consisted of infants without birth defects. The researchers identified affected infants who were born from 1968 through 1980 through the Metropolitan Atlanta Congenital Defects Program, a program that attempted to identify all individuals born with birth defects diagnosed during the first year of life. Furthermore, researchers chose for the case group only infants with serious structural congenital malformations, or birth defects, such as a substantial handicap, premature death, or a defect that required surgery or extensive medical care. The researchers included 7,133 infants with birth defects in the case group.

Erickson and his colleagues selected the control group infants from the 323,421 infants who were born in the Atlanta area during the same twelve-year period. With the aid of the State of Georgia Vital Records Unit, they chose infants that approximately matched the case group by race, year of birth, and hospital of birth, finally including 4,246 infants in the control group.

Following the formation of the case group and the control group, the researchers interviewed the infants' families over the course of a year, from 1982 to 1983. They explain the details of the interviews in the second subsection, "Study Data." The authors note that they located the parents by using information available the infants' birth certificates or medical records. The authors of the study also note that locating the parents was difficult due to the lack of accurate information. Upon locating the parents, the researchers asked them to participate in a study designed to learn about the causes of birth defects. Due to the controversy surrounding the Vietnam War and Agent Orange, the researchers did not initially mention either during the interviews to further avoid potential bias that might lead Vietnam veterans to over-report adverse health outcomes.

After a family agreed to participate, two interviewers questioned each mother and father over the phone. The first interviewer asked about the parent's reproductive history. The second interviewer asked about potential causes of birth defects, like exposure to certain chemicals in occupations, and the parents' history of chronic diseases and drug use. Because reproductive histories included descriptions of the infant's health, there was no way to conceal the case or control status of the infant in question from the first interviewer, which could potentially bias the interviewers conducting of the interview. To minimize interviewer bias, the second interviewer did not know the case or control-group status of the infant. If both mother and father agreed to complete interviews, then a total of four interviewers contacted one family, two for each parent. Of the 7,133 case-group infants, 4,929 mothers and 3,977 fathers completed interviews. Of the 4,246 control-group infants, 3,029 mothers and 2,426 fathers completed interviews. The authors note that a major reason that parents did not participate was because they were not able to locate them.

The researchers also instructed the interviewers to obtain a history of paternal military service during interviews with either parent. Erickson and his colleagues defined veterans as fathers who had served in the US military at any time, and Vietnam veterans as fathers who had served in Vietnam before the conception of their children. Interviewers asked fathers who identified themselves as Vietnam veterans if they believed they had been exposed to Agent Orange. Their answers were then referred to the Army Agent Orange Task Force, a panel of service specialists from the US Department of Defense, to assign each veteran an Exposure Opportunity Index (EOI) score.

The EOI score was a graded score from one to five, with one meaning limited opportunities for

exposure to Agent Orange, and five meaning high opportunities for exposure. A total of two EOI evaluations were assigned to each Vietnam veteran in the study, one according to their self-reports and one according to the veteran's military records. The second EOI score was determined by specialists who reviewed each Vietnam veteran's occupation, location, and time of service in Vietnam and compared them to military records of herbicide application. According to Erickson and his colleagues, it was difficult to verify the accuracy of the veterans' self-reports or the accuracy of the EOI scoring. Herbicide records that were available at the time were not made for health studies but for military records, meaning that the information was not intended to be used to estimate herbicide exposure and subsequent health effects. They conclude the second subsection by stating that despite those potential inaccuracies, they felt that the EOI scores were the only possible way to measure Agent Orange exposure at that time.

In the last subsection of the "Methods" section, titled "Analytic Approach," Erickson and his colleagues explain how they used the EOI scores. They first categorized all the birth defects that affected the case group infants into 96 categories. They then determined if any of the categories of birth defects was linked to a specific cohort, either Vietnam veterans in general or Vietnam veterans with a particular set of EOI scores. The groups included categories of broadly labeled defects, such as total nervous system defects and total respiratory tract defects, and specific defects, such as spina bifida and hydrocephalus, which are birth defects involving the brain, spine, and spinal cord. One group included all of the birth defects affecting the case group infants, aptly named "All Case Babies." Infants with more than one defect were included in each relevant group.

Within each of the 96 groups, the researchers sought to answer four questions relating to all US veterans, Vietnam veterans, the veterans' EOI scores, and the veterans' self-reported Agent Orange experiences. First, they determined whether the risk of fathering infants with birth defects was greater for all veterans (not just Vietnam veterans) than for non-veterans. The authors say that they chose that question because they thought that Vietnam veterans might be at increased risk of fathering infants with birth defects relative to other veterans, but at decreased risk relative to nonveterans.

The second question, about Vietnam veteran status asked whether Vietnam veterans were at greater risk than all other men for fathering infants with birth defects.

The third question evaluated whether the veterans' risk of fathering infants with birth defects was related to their EOI scores. The assessment was conducted twice, once with the EOI score obtained from military records and once with the EOI score derived from the veterans' self-reports.

Lastly, the researchers asked if there was a correlation between Vietnam veterans who reported that they had been exposed to Agent Orange, regardless of their EOI scores, and the health outcomes of their infant children. Regarding the last question, the authors considered the possibility that veterans might be biased when answering questions about Agent Orange. Specifically, men who had fathered children with birth defects might already believe that Agent Orange caused those birth defects, which may affect their answers regarding their exposure to Agent Orange and other herbicides. To account for this possibility, researchers evaluated the fourth question by comparing data on one type of defect with data on all other types of defects, assuming that a parent with a biased answer would only affect one category of birth defects, and not all categories.

The researchers evaluated each of the questions three times for each of the 96 categories. Using statistical methods, they determined each veteran's risk of fathering infants with birth defects. If Vietnam veterans had twice the risk as other men, their relative risk was 2.0. If the veterans' risk was half that of other men, their relative risk was 0.5. If Vietnam veterans were at greater risk, then there would be a higher percentage of Vietnam veterans among fathers of infants with birth defects, and a smaller percentage of Vietnam veterans in the control group.

The authors conclude the "Methods" section by summarizing three additional issues related to Vietnam military service that they evaluated in the study. They first determined if fathers of infants with particular birth defects were more frequently Vietnam veterans. Secondly, researchers assessed whether Vietnam veterans were at an increased risk of fathering multiple children with birth defects. Thirdly, they asked if Vietnam veteran fathers had contracted malaria in Vietnam, a tropical disease transmitted by mosquitoes that affected over 40,000 US soldiers during the war, and if vet-

erans had taken anti-malarial medicine. They asked about malaria because malaria or anti-malarial medicine might have been linked to birth defects.

In the second main section of the paper, titled "Results," the authors report the results of the interviews, their four questions, and the three supplementary issues they examined. Of the eligible families in both groups, 69.9% (7,958) of mothers and 56.3% (6,403) of fathers completed interviews. Approximately, an additional 1% of mothers and fathers completed partial interviews to the point that the interviewers obtained paternal military history. For the first question, which compared all veterans with nonveterans, approximately 38% of fathers in the case group were veterans, compared to approximately 39% of fathers in the control group. The relative risk was 0.94, meaning that veterans in general did not have increased risk for fathering infants with birth defects. Because Vietnam veterans and non-Vietnam veterans were not at increased risk, the researchers evaluated the remaining three questions by comparing Vietnam veterans' risks to those of nonveterans and veterans combined.

For the second question, Erickson and his colleagues report that when all types of defects were combined, 9.2% of case group fathers had served in Vietnam, compared to 9.5% of fathers in the control group. Because the proportions were similar, and the estimated relative risk was 0.97, the researchers concluded that the risk of Vietnam veterans for fathering infants with birth defects was not significantly different from that of other fathers. They found similar results in the remaining 95 groups of birth defects.

Lastly, the results of the third and fourth questions show that Vietnam veterans who had been assigned higher Agent Orange EOI scores or veterans who believed they had been exposed to Agent Orange did not have significantly higher risk of fathering infants with all birth defects combined. The results of all four tests across all 96 groups are displayed in a table that covered two pages of the journal article.

The four questions produced similar results in most defect groups. However, the authors of the study note several statistically significant findings. Vietnam veterans with higher EOI scores had a higher estimated risk for fathering infants with spina bifida, a defect characterized by an improperly formed spinal cord, which can cause partial or complete lower body paralysis. Veterans with a higher EOI score also had higher estimated risks for fathering infants with cleft lip with or without cleft palate, a birth defect marked by an improperly formed lip or mouth. Those with higher EOI scores also had higher risks of fathering infants with defects related to tumor growth, including benign tumors and cysts found under the skin. The researchers report that in the category "Total Sex Organ Defects," fathers of those infants were more likely to have reported that they contracted malaria while they were in Vietnam, pointing to an apparent association between paternal contraction of malaria and sex organ birth defects in the offspring.

In the final "Comment" section of the article, Erickson and his colleagues discuss the conclusions that they draw from the study. They consider their findings which did not suggest that Vietnam veterans were at greater risk than other men for fathering infants with all types of serious structural birth defects combined to be the most important conclusion from their study. The authors note that structural birth defects, when combined, affect roughly two to three percent of stillborn and live-born babies, and that statistically, two to three percent of infants born to returning Vietnam veterans were born with serious defects. Therefore, one could expect that a certain proportion of fathers in the case group would be Vietnam veterans, and that the presence of birth defects did not necessarily imply that there were external factors other than the usual rate that birth defects occur. The authors next say that the study does not prove if the cause of birth defects was a factor associated with service in Vietnam. They argue that their first conclusion regarding Vietnam veterans in general was based on relatively strong evidence, despite not addressing the actual cause of the birth defects in the study.

Based on the third and fourth questions, the authors also concluded that Vietnam veterans' risk for fathering infants with birth defects did not increase with higher EOI scores or with higher self-reported Agent Orange exposure. However, they stated that they considered that second conclusion regarding the association with Agent Orange to be based on considerably weaker evidence than the primary conclusion about Vietnam veterans in general, due to the potential inaccuracy of the

EOI scores. They note that to further study the association between increased risk of fathering infants with birth defects and Agent Orange exposure, researchers need to consider select groups of Vietnam veterans or specific types of defects. Despite the uncertain validity of the EOI scores, Erickson and his colleagues cite their use of the veterans' self-reports as a strength of the study.

The authors then address the statistically significant results of the study, prefacing their summary by saying that irregular results should be expected of any study with multiple hypotheses. Specifically, they highlight that a statistically significant result was not necessarily correlated with an increased or different risk of fathering an infant with a specific birth defect. Regarding the finding that veterans with higher EOI scores seemed more likely to father infants with spina bifida, the authors attribute the association with spina bifida to chance. This was because veterans with higher EOI scores were not found to have higher estimated risk for fathering infants with anencephalus, a related defect of spina bifida. The authors make the same attributions to chance occurred with congenital neoplasms and the orofacial defects that include cleft lip and cleft palate, due to statistical methods that pointed to an unknown factor that affected the study.

The authors contextualize their results by summarizing the results of related studies. At the time, there was only one other study published on the association of birth defects to Vietnam service, conducted by researchers at the Commonwealth Institute of Health at the University of Sydney, Australia. Titled "Case-Control Study of Congenital Anomalies and Vietnam Service," the authors of that study concluded that there was no increased risk of all types of structural birth defects combined among men who served in Vietnam in the Australian Army. Other studies had been conducted on the health effects of dioxins in non-military settings, like in herbicide factories, but no adverse human reproductive effects had been conclusively linked. And while the link had been solidified between maternal exposure to drugs and subsequent reproductive issues, Erickson and his colleagues note that the contribution of paternal exposures to birth defects had not been extensively investigated.

In the last paragraph of the paper, the authors state that only a limited number of studies had been published that focused on human populations with well-documented exposure to herbicides and dioxins. Due to the small scale of those studies, Erickson and his colleagues claim that the inconclusive findings might reflect the weaknesses of their study rather than a true lack of association. They reiterate their belief that the estimates of Agent Orange exposure were likely inaccurate, and therefore, their secondary conclusion regarding Agent Orange associated risks for Vietnam veterans was also weak. Erickson and his colleagues conclude the paper by stating that if Agent Orange exposure was indeed linked to increased risk, then the risk was either small, limited to select group of veterans, or limited to specific types of defects.

When the paper was published in the *Journal of the American Medical Association* in August of 1984, it was accompanied by an editorial by Bruce Dan, senior editor of the *Journal of the American Medical Association*. In the editorial, Dan included a brief overview of the use of herbicides in Vietnam, the toxicology of Agent Orange and the contaminant TCDD, and the reported health problems of veterans who had fought in Vietnam. He explained how congenital malformations could be related to a man or woman's exposure to chemicals. Dan argued that it was important to investigate the link between Vietnam service and the rate of birth defects because other factors aside from chemical exposure such as stress, poor nutrition, and alcohol or drug abuse could increase the incidence of birth defects. After summarizing Erickson and colleagues' paper, Dan concluded that it was unlikely that serious birth defects of Vietnam veterans' children were related to the fathers' Vietnam experience.

Nearly a year later, on 2 August 1985, the *Journal of the American Medical Association* published a "To the Editor" letter by Theodore Sterling and Anthony Arundel, two researchers at Simon Fraser University in British Columbia, Canada. The letter, which shared the same title as Erickson's paper, stated that there was a difference between studying birth defects among children of Vietnam veterans, and studying birth defects among children of Vietnam veterans exposed to Agent Orange. Sterling and Arundel noted that the Australian study and CDC study focused on the Vietnam link more than the Agent Orange link. The authors also noted that the CDC's findings of higher than expected rates of cleft palate and spina bifida should not be dismissed as chance phenomena. They considered the results significant because of other studies which had found higher rates of cleft

palate, spina bifida, and other birth defects related to improper neural tube disclosure, after exposure or possible exposure to 2,4,5-trichlorophenoxyacetic acid, one of the main components of Agent Orange. Sterling and Arundel expressed concern with Dan's editorial, which they said suggested that there was no basis for a link between Agent Orange and birth defects. They concluded that the possible relationship between Agent Orange exposure and birth defects warranted further research, either by studying exposed US Vietnam veterans, or studying exposed and unexposed people in Vietnam.

The CDC study by Erickson and colleagues was the first US report to assess the association between Vietnam military service and serious congenital anomalies. In the late 1980s, the CDC conducted a larger study in conjunction with the Veterans Administration called the Vietnam Experience Study. The third part of that study focused on the reproductive outcomes and child health of Vietnam veterans, during which interview data also revealed higher numbers of cerebrospinal malformations (like spina bifida) in the children of Vietnam veterans. However, the Vietnam Experience Study authors concluded that there were no significant differences in the occurrence of birth defects between children of Vietnam and non-Vietnam veterans, and that their findings were consistent with previous epidemiologic studies, including the one by Erickson and his colleagues.

In the early 1990s, US Congress enacted Public Law 102-4, more commonly called the Agent Orange Act of 1991, which directed the US National Academy of Sciences to publish reports every two years that reviewed and evaluated newly published scientific literature regarding the effects of dioxin exposure, in particular pertaining to Vietnam veterans and their families' health outcomes. In the 1996 report by the National Academy of Sciences Institute of Medicine committee, the authors acknowledged a link between Agent Orange exposure and the occurrence of spina bifida in children. The conclusion led the US Veterans Administration to provide disability benefits to Vietnam veterans' children with spina bifida, marking the first time that the Veterans Administration provided compensation to veterans' family members.

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