Science

The Fog of War

Fifty years after the Vietnam War, researchers are still struggling to document the long-term health effects of the massive spraying of Agent Orange and other herbicides

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Nearly 2 decades ago, more than 240 women who had recently given birth in Da Nang, Vietnam, got an unusual request from visiting nurses checking on their newborns: Could we collect a small sample of your breast milk?

The mothers had volunteered for a study scientists hoped would answer a question that had haunted Vietnam since what it calls the Resistance War Against America ended in 1975: Had the U.S. military's massive aerial spraying of vegetation-killing chemicals during the conflict put children's health at risk?

By the time the milk-collecting effort began in 2008, researchers already knew those herbicides—collectively called Agent Orange, after the orange stripe painted on the barrels holding one formulation—were tainted with a highly toxic dioxin, a long-lived chemical linked to an array of human health problems. Postwar surveys had found that relatively high concentrations of dioxin lingered in some of Vietnam's soils and aquatic sediments, especially near former U.S. air bases—such as the one in Da Nang—that had handled vast volumes of the chemicals. And Agent Orange had been anecdotally linked to reports of birth defects in communities exposed to the spraying, which lasted from 1961 to 1971.

Vast swaths of forest and farmland in South Vietnam were denuded by the U.S. military's spraying of herbicides from 1961 to 1971.Archive Image/Alamy

As years went by, Vietnam asserted that those harmed by Agent Orange included the second-, third-, and even fourth-generation relatives of those who experienced the spraying, because of dioxin lingering in the environment or inherited health effects. The country put birth defects at the center of its descriptions of the horrors of Agent Orange. But few studies had attempted to rigorously examine a link, until the Da Nang work. Led by environmental health scientist Muneko Nishijo of Kanazawa Medical University and public health specialist Tai Pham-The of the Vietnam Military Medical University, it aimed to document dioxin levels in the milk of new mothers, then follow their children as they matured.

Now, Vietnam is preparing to mark the 50th anniversary of the event that ended the war—the capture of Saigon, now Ho Chi Minh City, by North Vietnamese and Viet Cong forces on 30 April 1975. Yet that study remains one of the few ongoing research efforts on the long-term health effects of the bitter conflict, which cost the lives of some 3.3 million Vietnamese and nearly 60,000 U.S. service members. It did not resolve the birth defects question. But Nishijo and Tai did find evidence that the chemical can affect brain development in exposed children, and others are studying how the conflict is still affecting the physical and mental health of those who lived through it (see sidebar, below).

By now, most Vietnamese have no memory of the war, as the majority of the nation's 101 million people were born after it ended. And finding support for studies to understand the war's continuing impact is proving increasingly difficult, as neither the United States nor Vietnam appears eager to revisit that era. But, "The ongoing burden of disease among exposed populations means that Vietnam's dioxin legacy remains a significant public health challenge," says environmental health scientist Tran Thi Tuyet-Hanh of the Hanoi University of Public Health.

The Vietnam War marked the biggest deployment of herbicidal warfare the world has ever seen. Between 1961 and 1971, lumbering aircraft sprayed an estimated 74 million liters of the chemicals over South Vietnam as well as border areas of Laos and Cambodia. The goal was to strip foliage from mangrove swamps and dense forests that were providing cover for North Vietnamese and Viet Cong troops, and to destroy crops they relied on for food.

Looking for links

A 2018 U.S. National Academies report found "sufficient" or "suggestive" evidence linking 19 conditions to herbicide exposure.

Sufficient evidence

- Soft-tissue sarcoma
- Non-Hodgkin and Hodgkin lymphoma
- Chronic lymphocytic leukemia
- Chloracne
- Hypertension

Suggestive evidence

- Laryngeal, lung, and bladder cancer
- Multiple myeloma
- Parkinson's disease

- Ischemic heart disease
- Stroke
- Hypothyroidism

No consensus

- Type 2 diabetes

DATA: NATIONAL ACADEMIES OF SCIENCES, ENGINEERING, AND MEDICINE. 2018. *VETERANS AND AGENT ORANGE: UPDATE 11 (2018)*. HTTPS://DOI.ORG/10.17226/25137

The weapons of choice were called the rainbow herbicides—a half-dozen formulations identified by names such as Agent Pink and Agent White, after the colors used to mark barrels. Agent Orange, which became the most notorious, was a 50-50 blend of two commercially available herbicides, 2,4-dichlorophenoxyacetic acid and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T). The defoliants were believed to be harmless to humans, and U.S. troops typically handled them without wearing protective gear.

By the late 1960s, however, lab experiments showed 2,4,5-T could cause abnormalities and stillbirths in mice, and there were reports of human birth defects in sprayed areas of Vietnam. Later it became clear that the herbicide manufacturing process introduced a particularly toxic dioxin, known as 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), into Agent Orange and other herbicides. Four years before the war ended, the U.S. abandoned its decadelong spraying campaign amid mounting international condemnation and concerns about safety.

Today, there is broad consensus that dioxin poses serious health risks to those directly exposed, including Vietnamese citizens and soldiers as well as members of the armed forces of the U.S. and other countries that aided it during the war: South Korea, Australia, and New Zealand. That consensus rests, in part, on efforts by the U.S. government to assess how exposure affected the health of U.S. veterans. In 1992, the Department of Veterans Affairs asked the Institute of Medicine, now part of the U.S. National Academies of Sciences, Engineering, and Medicine (NASEM), to review the scientific literature and provide biennial updates. The last of those reports, *Veterans and Agent Orange,* appeared in 2018 and identified 19 cancers and other conditions with “sufficient” or “suggestive” evidence of an association with exposure to the herbicides (see box, above). Vietnamese investigators separately produced a similar list.

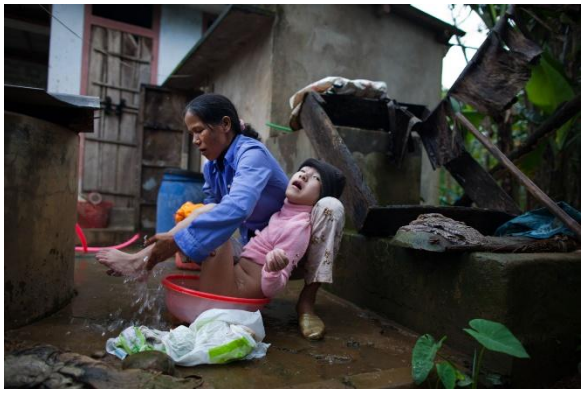
But such studies largely left open one of the most visible and contentious questions surrounding Agent Orange: whether the compounds pose risks not just for those who were directly exposed, but for their children.

The concern about future generations was prompted, in large part, by the worrisome staying power of TCDD, the dioxin that contaminated Agent Orange. Unlike the herbicide itself, which decomposes within hours to days, TCDD can survive up to 3 years in soil that is exposed to sunlight. If leached into river or pond sediment, it can have a half-life of more than 100 years—more than enough time to be picked up by fish, ducks, and other animals that people eat. (People can also inhale contaminated dust and absorb dioxin through the skin.) Once in the human body, dioxin can lodge in breast and other fatty tissue and have a half-life of 7 to 11 years. It can also contaminate breast milk and be passed to breastfeeding babies.

Since the 1970s, numerous animal studies have found that fetuses exposed to dioxin can exhibit a wide range of birth defects and developmental problems, suggesting an impact on human fetuses is biologically plausible. But documenting it has proved difficult.

Because of the Agent Orange spraying, Vietnam was the obvious place to seek an answer. In 2003, the U.S. National Institute of Environmental Health Sciences (NIEHS) approved a 5-year, $3.5 million study proposed by public health physician David Carpenter of the University at Albany. It planned to analyze dioxin levels in the blood of 300 Vietnamese mothers of babies with birth defects, using 300 mothers of healthy infants as controls. But NIEHS canceled the study in 2005 after failing to agree on research protocols with Vietnam's Ministry of Health.

The next year, a team led by Tuan Van Nguyen, then at the Garvan Institute of Medical Research, published a meta-analysis of 22 studies, including unpublished Vietnamese-language reports, that suggested mothers exposed to Agent Orange were twice as likely to have children with birth defects as those not exposed. But that conclusion, reported in the *International Journal of Epidemiology*, proved controversial. In a commentary in the same journal, toxicologist Arnold Schecter of the University of Texas and surgeon John Constable of Harvard Medical School criticized the paper for relying on old, non–peer-reviewed publications. "We know of no non-Vietnamese studies linking herbicide or dioxin exposure to congenital malformations other than spina bifida and anencephaly," the pair wrote. (In 2014, the NASEM committee that produced that year's update to *Veterans and Agent Orange* reviewed additional evidence and concluded it was "inadequate or insufficient" to link Agent Orange to any birth defects, including spina bifida.)



In Vietnam, the government has asserted that contamination from herbicide spraying by the U.S. military is responsible for birth defects. PAULA BRONSTEIN/GETTY IMAGES

Nguyen, now at the University of Technology Sydney, says that although their work suggested an association between Agent Orange exposure and birth defects, many of the studies they drew on were observational. As a result, "We avoided causal conclusions." But more rigorous cohort studies that tracked individuals in a way that would rule out confounding factors, such as maternal age and exposure to other chemicals, could yield firmer conclusions, he says.

A good opportunity to launch those studies was missed, Nguyen says. By the mid-2000s, Vietnamese and U.S. researchers had measured the dioxin burdens of a significant number of individuals from across Vietnam, which could have enabled a large-scale study of the birth defects question. But Vietnamese authorities never acted on Nguyen's suggestion to use those data. "The study was entirely feasible, yet it was never conducted, which was deeply disappointing," Nguyen says.

Several factors explain the lackluster support, scientists say. One is that the topic "is extremely political" in both Vietnam and the U.S., Carpenter says. For example, if his 2003 study "had shown what we expected"—that herbicide exposure was linked to birth defects—the U.S. might have been "expected to pay reparations to Vietnamese children." Alternatively, if it had found no link, that might have "embarrassed" the Vietnamese government, which has long highlighted birth defects as Agent Orange's most prominent harm.

At this point, Carpenter says, “It looks increasingly hopeless to think that an adequate study [of the birth defects question] will ever be funded and done.”

For the moment, Nishijo’s and Tai’s breast milk study is the only ongoing epidemiological study focusing on dioxin in Vietnam, Nishijo notes. Launched in Da Nang, it has since expanded to a second cohort near the former Bien Hoa Air Base, another hot spot, and a control group. But the study is unlikely to provide a definitive answer to the birth defects question. “Our cohort is too small to investigate congenital anomalies,” because they occur rarely, Nishijo says.

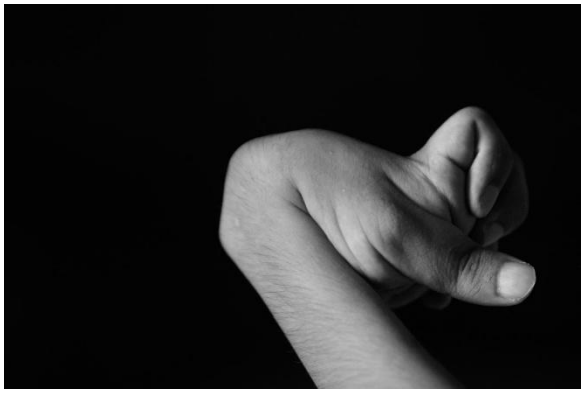
Still, in dozens of papers published over the past 15 years, the team has documented other links. In particular, they have found that a high level of dioxin in a mother’s milk—a proxy for fetal exposure—is associated with slower physical growth and lagging neurodevelopment in their children. Boys exhibit learning difficulties, for example, whereas girls show attention deficit hyperactivity disorder and autism.

The papers “provide strong evidence” that living near sites contaminated by Agent Orange can result in high dioxin body burdens that are associated with behavioral disorders in children, says Steven Stellman, an epidemiologist now retired from Columbia University who was long involved in Agent Orange studies.

If funding allows, Nishijo and Tai intend to keep following the children as they age. That could reveal links between dioxin exposure and cancers and other diseases that manifest later in life.

In the meantime, other researchers say there’s another issue surrounding the long-term health impacts of Agent Orange that could still be studied—if funders are willing to step forward. It is the question of whether exposure has caused fundamental biological changes in people that can be handed down from generation to generation.

Vietnamese scientists and officials contend they are seeing such multigenerational effects resulting in birth defects several generations after exposure. And although the authors of the 2018 NASEM report concluded there was “inadequate or insufficient evidence” of epigenetic effects, they strongly encouraged more study of the issue.



The deformed hand of Nguyen Van Danh, whose father and grandparents lived in areas sprayed with herbicides during the Vietnam War. Establishing direct links between herbicide exposure and birth defects has proved difficult. Kuni Takahashi/Getty Images

Here, too, there is suggestive evidence from animal experiments. Michael Skinner, a biologist at Washington State University, has reported that, in rodents, genetic changes and adult-onset diseases linked to dioxin exposure can be seen in fourth-generation descendants.

Recent human research also lends support to the idea. Cristina Giuliani, a biological anthropologist at University of Bologna, and colleagues at the Hue University of Medicine and Pharmacy and the University of California (UC), Riverside focused on an epigenetic mechanism called DNA methylation and how it

affected the expression of one particular gene, *CYP1A1*, which has a role in breaking down toxic compounds, making them easier to be eliminated from the body. “TCDD is different as it cannot be fully detoxified and its presence further stresses the detoxification system,” she says. In a 2018 *Environmental Pollution* paper, they reported that the offspring of Vietnamese parents exposed to Agent Orange shared a distinctive *CYP1A1* DNA methylation signature that was not seen in the children of parents with no exposure.

Giuliani is careful to note that the study “does not experimentally demonstrate that exposure to dioxin is transmitted to descendants.” And it does not address the question of whether any changes are harmful, beneficial, or neutral.

Getting a firmer grip on those issues, researchers say, would require epigenetic studies comparing several generations of exposed and nonexposed populations. But there are “no studies like that yet,” Skinner says. And finding the funding to conduct such studies in Vietnam, he says, “would be difficult … due to the politics of the situation.”

The 50th anniversary of the end of the war is likely to draw renewed attention to the Agent Orange era. But many researchers doubt it will lead to a substantial surge in scientific activity. One obstacle is that Vietnam now has “more pressing environmental health issues,” such as increasingly severe air pollution from sources including the widespread burning of plastic waste, says David Biggs, an environmental historian at UC Riverside who has studied the Agent Orange controversy.

Another hurdle is that the impact of Agent Orange is fading. In the early 2000s, the Vietnam Red Cross Society estimated 3 million people were affected by the spraying and lingering contamination. But those who were directly exposed to the spray are dying, and ongoing exposure “will become less and less because this dioxin no longer exists in the environment” as it breaks down, says Le Ke Son, a toxicologist who led the Vietnamese government’s efforts to deal with the herbicides. The U.S. has also paid to clean up some contaminated sites, although one or two hot spots still persist. (President Donald Trump’s administration suspended but later restored funding for a cleanup of the Bien Hoa site.) And even if biological changes due to exposure can be inherited, “those born with severe disabilities are less likely to marry and have children,” says Charles Bailey, who spearheaded the Ford Foundation’s efforts to address Agent Orange issues in Vietnam in the early 2000s.

Still, even 50 years on, Agent Orange casts a dark shadow over Vietnam. And Carpenter, for one, believes “we are missing a very important opportunity to understand more about the risks.”

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https://www.science.org/content/article/vietnam-health-effects-agent-orange-remain-uncertain-50-years-later