THE NATIONAL ACADEMIES REPORT
Veterans and Agent Orange: Update 11

Statement of Dr. Karl Kelsey
Professor of Epidemiology, Professor of Pathology and Laboratory Medicine
Brown University.

before the
Committee on Veterans' Affairs
U.S. Senate

March 10, 2021

Chairman Tester, Ranking Member Moran, and members of the Committee, thank you for the opportunity to testify today. My name is Dr. Karl Kelsey and I am a physician as well as Professor of Epidemiology and Professor of Pathology and Laboratory Medicine at Brown University. I'm speaking to you today in my capacity as a member of a committee formed by the National Academies of Sciences, Engineering, and Medicine (National Academies) that completed the most recent in a series of reports—published in November 2018—assessing the evidence between exposure to Agent Orange and the other herbicides used in the Vietnam War and adverse health effects. I also served on the committees responsible for three previous reports in this series.

The National Academy of Sciences was created more than 150 years ago through a congressional charter signed by Abraham Lincoln in order to serve as an independent, authoritative body outside the government that could advise the nation on matters pertaining to science and technology. Every year, approximately 6,000 Academies members and volunteers serve pro bono on consensus study committees or convening activities. The National Academies do not advocate for specific policy positions. Rather, they enlist the best available expertise across disciplines to examine the evidence, reach consensus, and identify a path forward. National Academies reports, proceedings and other publications are available via the web in PDF form without charge.

The National Academies have a long history of advising the federal government on the health effects of military service in general and on the effects of in-theater exposures resulting from military activities in particular. In addition to the 12-report *Veterans and Agent Orange* (VAO) series, there have also been several focused reports that have examined the effects of herbicide exposures in Vietnam veterans. A list of the National Academies reports related to health issues in Vietnam veterans is included in the materials I have submitted for the committee's attention.

I'd now like to address the National Academies' most recent findings on this topic. I was asked to focus my testimony on the epidemiologic evidence of exposure to the herbicides and hypertension.

From 1962 to 1971, the U.S. military sprayed herbicides over Vietnam for tactical purposes. The most-used chemical mixture sprayed was Agent Orange, which at the time of use was contaminated with 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), the most toxic form of dioxin.

Concerns from Vietnam veterans about their own—and their children's—health, as well as emerging evidence on ill effects of exposure to Agent Orange, led Congress to enact the Agent Orange Act of 1991, which directed the U.S. Department of Veterans Affairs (VA) to ask the National Academies to comprehensively evaluate scientific and medical information regarding the health effects of exposure to Agent Orange, other herbicides used in Vietnam, and the various components of those herbicides, including TCDD. The first report was published in 1994, and Congressionally mandated updates were published approximately every 2 years since. The most recent report, *Update 11 (2018)*, presents the committee's analysis of peer-reviewed, scientific reports published between September 30, 2014, and December 31, 2017.

For each association between a specific health outcome and exposure to TCDD and other chemicals present in the herbicides used by the military in Vietnam, the study committee was asked to consider three factors: whether a statistical association with herbicide exposure exists, taking into account the strength of the scientific evidence and the appropriateness of the statistical and epidemiologic methods used to detect the association; the increased risk of disease among those exposed to herbicides during service in the Republic of Vietnam during the Vietnam era; and whether there exists a plausible biological mechanism or other evidence of a causal relationship between herbicide exposure and the disease.

In accord with Congress's mandated presumption of herbicide exposure of all Vietnam veterans, VAO committees have used Vietnam-veteran status as a proxy for herbicide exposure when no more specific exposure information is available. To anticipate the health conditions associated with aging and to obtain additional information potentially relevant to the evaluation of health effects in Vietnam veterans, the committees have reviewed studies of other groups potentially exposed to the constituents present in the herbicide mixtures used in Vietnam.

VAO committees classify the strength of the evidence regarding the association between exposure to the chemicals of interest and health outcomes into four categories: sufficient, limited or suggestive, inadequate or insufficient, and no association. The classifications are based on the committee's evaluation of the epidemiologic literature and reflect their judgment of the relative certainty of the association between the outcome and exposure to the herbicides used in Vietnam or to any of their components or contaminants. The assessment of the evidence for each presented health outcome, also takes into account information from the already-established

evidence base. Over the sequence of reviews, evidence has accrued and resulted in reclassifying several health outcomes into a different category of association.

As mandated by the Agent Orange Act, the distinctions among categories are based on statistical association and not on strict causality. Our committee was directed to review the scientific data, not to recommend VA policy; therefore, the conclusions reported are not intended to imply or suggest policy decisions. The conclusions are related to the associations between exposure and outcomes in human populations, not to the likelihood that any individual's health problem is associated with or caused by the herbicides in question. A summary of our conclusions regarding the strength of evidence for all outcomes considered and definitions of the classifications is presented in the "Summary Table" document that is included in the materials submitted for this committee's attention.

Among the findings, the National Academies' committee concluded that the available medical and scientific information constitutes sufficient evidence of an association between exposure to at least one of the chemicals of interest and hypertension. Hypertension, which was defined as blood pressure above 140/90 mmHg when the reviewed studies were published, affects more than 70 million adult Americans and is a major risk factor for coronary heart disease, myocardial infarction, stroke, and heart and renal failure. The major quantifiable risk factors for hypertension are well established and include family history, age, sex, race, obesity, reduced nephron number, high dietary salt intake, tobacco use, excessive alcohol intake, and physical inactivity. The strongest conclusions regarding a potential increase in the incidence of hypertension come from studies that have controlled for these risk factors. The Centers for Disease Control and Prevention estimates that in the United States, 64% of men and 69% of women ages 65–74 years have hypertension.

The National Academies' committee responsible for the *Update 2006* report began evaluating hypertension separately from other circulatory diseases and concluded that there was limited or suggestive evidence of an association with exposure to the chemicals and herbicides of interest. That decision was based primarily on consistent evidence from several studies of Vietnam veterans that consistently reported an association between increased levels of serum dioxin and increased prevalence of hypertension. Other studies of U.S. Vietnam veterans that did not use serum dioxin concentrations as markers of exposure also reported an increased

prevalence of hypertension associated with presumed exposure to herbicides. Additional evidence reviewed by the committees responsible for *Update 2008*, *Update 2010*, *Update 2012*, and *Update 2014* reaffirmed that level of evidence of association. The studies of Vietnam veteran cohorts from other nations and occupational cohorts reviewed by previous VAO Update committees had mixed results, with reports of both increased and decreased risk, but few reached the level of statistical significance. Similar mixed and not statistically significant findings were reported for the studies of other exposed populations that have been reviewed. A summary of the results from epidemiologic studies related to circulatory disorders, including hypertension, that have been reviewed in the VAO series have been included in the materials submitted for the committee's attention.

The *Update 11* committee reviewed six new studies of exposure to the chemicals of interest and hypertension that had been published since the previous update. The decision to change the classification from limited or suggestive evidence of an association to sufficient evidence of an association by the *Update 11* committee was motivated in large part by a 2016 paper by VA researchers Yasmin Cypel and colleagues[1]. These investigators conducted a study of U.S. Vietnam veterans (specifically, the Army Chemical Corps [ACC]), that was characterized by a large sample size, appropriate controls, and validated health endpoints. The statistical analyses conducted were robust, included several levels of exposure (herbicide sprayers and non-sprayers and Vietnam-deployed and non-Vietnam-deployed) used state-of-the-art methods, and adjusted for relevant confounders. The study clearly showed that self-reported hypertension rates were the highest among those military personnel with the greatest opportunity for exposure to the chemicals of interest: 81.6% for Vietnam-deployed sprayers compared with 77.4% of non-Vietnam deployed sprayers, 72.2% for Vietnam-deployed non-sprayers, and 64.6% for non-Vietnam-deployed non-sprayers (64.6%). Among Vietnam-deployed veterans, there was a statistically significantly elevated association between the odds of hypertension for sprayers versus non-sprayers that remained after an adjustment for potential confounders. Similarly, for those veterans who did not deploy to Vietnam, self-reported hypertension was significantly elevated among sprayers compared with non-sprayers.

[1] Cypel YS, Kress AM, Eber SM, Schneiderman AI, Davey VJ. Herbicide Exposure, Vietnam Service, and Hypertension Risk in Army Chemical Corps Veterans. *J Occup Environ Med.* 2016;58(11):1127-1136. doi:10.1097/JOM.0000000000000876.

Although serum TCDD concentrations were not available for all participants and were collected at least 25 years after Vietnam-era service, for those with serum TCDD levels available, self-reported herbicide spray status had high agreement with the measured levels. The highest mean serum TCDD level was observed among sprayers deployed to Vietnam, and the lowest mean TCDD level was found for non-Vietnam non-sprayers, as would be expected, with a significant dose–response association. Likewise, there was high agreement (89%) between self-reported hypertension and in-person blood pressure measurements and medical records review for a subsample of study participants. The analyses controlled for important risk factors for hypertension, including age, race (white versus others), body mass index, tobacco smoking status, rank, Vietnam service status, and alcohol intake, but did not collect information on (and therefore did not control for) other risk factors such as diabetes, a family history of hypertension, and dietary intake of sodium and fat. A major strength of this analysis was using the non-Vietnam-deployed ACC veterans as a comparison group because they were similar to members of the study group with respect to branch, length and time period of service, military occupation, and duties except for deployment in Vietnam, which has the effect of minimizing unmeasured exposures and confounders of concern and bias. Additionally, because all of the men who served in ACC units were stationed at Fort McClellan for at least some time, and Fort McClellan is in close proximity to Anniston, Alabama, where Monsanto operated a plant that produced polychlorinated biphenyls, which have activity related to dioxin, all ACC veterans were likely exposed to at least low levels of these and other chemicals. Therefore, comparisons using deployed and non-deployed ACC men are likely to be biased toward the null due to this baseline of increased exposure, but despite that, the adjusted effect estimate when Vietnam-deployed sprayers were compared with non-Vietnam deployed non-sprayers was still more than twice as high, precise, and statistically significant. Although the exact types and quantities of the various chemicals these ACC veterans were possibly exposed to during the Vietnam War are unknown and may include chemicals other than the herbicides (such as insecticides, diesel and jet fuels, cleaning solvents, tear gas, napalm, and antimalarial medications), there is statistically significant support for an association between herbicide exposure and self-reported, physician-diagnosed hypertension.

The five additional epidemiologic studies reviewed in *Update 11* that examined hypertension as an outcome were two occupational and three environmental exposure investigations. Each of

these has one or more significant study design deficiencies as compared to the Cypel and colleagues analysis and would not be considered adequate to change the level of association individually. However, at least a portion of the effect model results corroborate the positive, elevated risk between exposure to the chemicals of interest and hypertension using a variety of study designs, populations, and measurements of exposure. Recent biological mechanistic research reviewed by our committee also showed evidence for dioxin's impact on hypertension via effects on gene expression, vascular function, and lipid glucose metabolism. Therefore, when the totality of evidence was considered, we found that this body of literature constituted sufficient evidence of an association.

This is only a brief summary of our work—the complete *Update 11* report is available for free download in PDF format from the National Academies Press website: nap.edu. I've also submitted a copy of the report highlights with my testimony today.

Thank you for the opportunity to testify. I would be happy to address any questions that you might have.

Additional Documents Accompanying Testimony:

Reports from the National Academies of Sciences, Engineering, and Medicine that Assess Exposure to Herbicides or Health Outcomes Among Vietnam Veterans

Table: Summary of All Outcomes Addressed in *Veterans and Agent Orange: Update 11* by category of association

Summary of the results from epidemiologic studies related to circulatory disorders that have been reviewed in the *VAO* series

Veterans and Agent Orange: Update 11 Report Highlights