

statistically significant, are capable of replication, and withstand peer review.” Simply comparing the number of studies which report a positive relative risk to the number of studies which report a negative relative risk for a particular condition is not a valid method for determining whether the weight of evidence overall supports a finding that there is or is not a positive association between herbicide exposure and the subsequent development of the particular condition. Because of differences in statistical significance, confidence levels, control for confounding factors, bias, and other pertinent characteristics, some studies are clearly more credible than others, and the Secretary has given the more credible studies more weight in evaluating the overall weight of the evidence concerning specific diseases.

NAS issued its initial report, entitled “Veterans and Agent Orange: Health Effects of Herbicides Used in Vietnam,” (VAO) on July 27, 1993. The Secretary subsequently determined that a positive association exists between exposure to herbicides used in the Republic of Vietnam and the subsequent development of Hodgkin’s disease, porphyria cutanea tarda, multiple myeloma, and certain respiratory cancers; and that there was no positive association between herbicide exposure and any other condition, other than chloracne, non-Hodgkin’s lymphoma, and soft-tissue sarcomas, for which presumptions already existed. A notice of the diseases that the Secretary determined were not associated with exposure to herbicide agents was published on January 4, 1994. (See 59 FR 341 [1994].)

NAS issued its second report, entitled “Veterans and Agent Orange: Update 1996” (Update 1996), on March 14, 1996. The Secretary subsequently determined that a positive association exists between exposure to herbicides used in the Republic of Vietnam and the subsequent development of prostate cancer and acute and subacute peripheral neuropathy in exposed persons. The Secretary further determined that there was no positive association between herbicide exposure and any other condition, other than those for which presumptions already existed. A notice of the diseases that the Secretary determined were not associated with exposure to herbicide agents was published on August 8, 1996. (See 61 FR 41442 (1996).)

NAS issued a third report, entitled “Veterans and Agent Orange: Update 1998” (Update 1998), on February 11, 1999. The focus of this updated review was on new scientific studies published

since the release of Update 1996 and updates of scientific studies previously reviewed. After NAS issued Update 1998, the Secretary determined that there was no positive association between herbicide exposure and any other condition, other than those for which presumptions already existed. A notice of the diseases that the Secretary determined were not associated with exposure to herbicide agents was published on November 2, 1999. (See 64 FR 59232 [1999].)

At VA’s request, NAS issued a special interim report, “Veterans and Agent Orange: Herbicide/Dioxin Exposure and Type 2 Diabetes” (VAO: Diabetes) on October 11, 2000. NAS concluded “there is limited/suggestive evidence of an association between exposure to the herbicides used in Vietnam or the contaminant dioxin and Type 2 diabetes.” NAS based its conclusion on the totality of the scientific evidence on this issue, not one particular study. (VAO: Diabetes.) After considering all of the evidence, the Secretary determined that there is a positive association between exposure to herbicides and Type 2 diabetes and, therefore, a presumption of service connection was warranted. (See 66 FR 2376 (2001).)

NAS issued a fourth report, entitled “Veterans and Agent Orange: Update 2000” (Update 2000), on April 19, 2001. The focus of this updated review was on new scientific studies published since the release of Update 1998 and updates of scientific studies previously reviewed. After NAS issued Update 2000, the Secretary determined that there was no positive association between herbicide exposure and any other condition, other than those for which presumptions already existed. A notice of the diseases that the Secretary determined were not associated with exposure to herbicide agents was published on June 24, 2002 (See 67 FR 42600–608).

NAS issued its fifth report, entitled “Veterans and Agent Orange: Update 2002” (Update 2002) on January 23, 2003. The focus of this updated review was on new scientific studies published since the release of Update 2000, and to review the studies previously reviewed along with the newest scientific evidence. The Secretary subsequently determined that a positive association exists between exposure to herbicides used in the Republic of Vietnam and the subsequent development of chronic lymphocytic leukemia (CLL) in exposed persons. A proposed rule to establish a presumption of service connection for CLL was published in the **Federal Register** of March 26, 2003 (See 68 FR 14567). The Secretary also determined

that there is no positive association between herbicide exposure and hepatobiliary cancers, nasopharyngeal cancer, bone and joint cancer, breast cancer, cancers of the female reproductive system, urinary bladder cancer, renal cancer, testicular cancer, leukemia (other than CLL), abnormal sperm parameters and infertility, Parkinson’s disease and parkinsonism, amyotrophic lateral sclerosis (ALS), chronic persistent peripheral neuropathy, lipid and lipoprotein disorders, gastrointestinal and digestive disease including liver toxicity, immune system disorders, circulatory disorders, respiratory disorders (other than certain respiratory cancers), skin cancer, cognitive and neuropsychiatric effects, gastrointestinal tract tumors, brain tumors, AL amyloidosis, endometriosis, adverse effects on thyroid homeostasis, and any other condition for which the Secretary has not specifically determined a presumption of service connection is warranted. This notice, pursuant to 38 U.S.C. 1116(c)(1)(B), summarizes the scientific data reviewed by NAS in its Update 2002, and conveys the Secretary’s determination regarding no positive association between herbicide exposure and the above-cited conditions.

NAS, in Update 2002, assigns hepatobiliary cancers, nasopharyngeal cancer, bone and joint cancer, breast cancer, cancers of the female reproductive system, urinary bladder cancer, renal cancer, testicular cancer, leukemia (other than CLL), abnormal sperm parameters and infertility, Parkinson’s disease and parkinsonism, chronic persistent peripheral neuropathy, lipid and lipoprotein disorders, gastrointestinal and digestive disease, immune system disorders, circulatory disorders, respiratory disorders (other than certain respiratory cancers), skin cancer, cognitive and neuropsychiatric effects, AL amyloidosis, endometriosis, and adverse effects on thyroid homeostasis to a category labeled inadequate/insufficient evidence to determine whether an association exists. This is defined as meaning that the available studies are of insufficient quality, consistency, or statistical power to permit a conclusion regarding the presence or absence of an association with herbicide exposure. In Update 2002, NAS assigned gastrointestinal tract tumors and brain tumors to a category labeled limited or suggestive evidence of no association. This is defined as meaning that the available studies are mutually consistent in not showing a positive association between exposure to