

NAS reviewed a number of new studies for Update 2002. A follow up to an occupational study reviewed in Update 2000 published results on the reproducibility of the self-reported data on farm exposures to potentially hazardous agents such as pesticides. (Duell EJ, Millikan RC, Savitz DA, Schell MJ, Newman B, Tse CJ, Sandler DP. 2001. Reproducibility of reported farming activities and pesticide use among breast cancer cases and controls: A comparison of two modes of data collection. *Annals of Epidemiology* 11(3):178–185) It was found that the farming-exposure information was generally reproducible, which provided some assurance that the prior conclusion of no overall excess risk of breast cancer was not due to measurement error in the exposure assessment.

An environmental study of the joint effects of all congeners of polychlorinated biphenyls (PCBs) (Holford TR, Zheng T, Mayne ST, Zahm SH, Tessari JD, Boyle P. 2000. Joint effects of nine polychlorinated biphenyl (PCB) congeners on breast cancer risk. *International Journal of Epidemiology* 29 (6):975–82) showed that total PCB was not significantly associated with breast cancer risk. NAS noted, however, that significant protective effects were detected for potential antiestrogens and a dioxin-like congener. This study was consistent with results of previously reported studies. General population controls were not used, which limited the external validity of the results.

The relationship between the relatively high dioxin concentrations in Chapaevsk, Russia and breast cancer incidence and related mortality was studied in Revich *et al.* (2001). The incidence rate of female breast cancer, age-adjusted to the Russian standard population, was higher in Chapaevsk in all age groups than in Russia and the Samara region. NAS noted that the lack of adjustment for such risk factors as family size, breastfeeding, alcohol use, body-mass index and fat consumption was one of the main weakness of this study.

Two environmental studies provided evidence of a relationship between the development of breast cancer and increased concentrations of PCB congeners that have dioxin-like activity. (Aronson KJ, Miller AB, Woolcott CG, Sterns EE, McCready DR, Lickley LA, Fish EB, Hiraki GY, Holloway C, Ross T, Hanna WM, SenGupta SK, Weber J-P. 2000. Breast adipose tissue concentrations of polychlorinated biphenyls and other organochlorines and breast cancer risk. *Cancer Epidemiology, Biomarkers and*

Prevention 9(1):53–63; Demers A, Ayotte P, Brisson J, Dodin S, Robert J, Dewailly E. 2002. Plasma concentrations of polychlorinated biphenyls and the risk of breast cancer: A congener-specific analysis. *American Journal of Epidemiology* 155(7):629–635) NAS noted that the external validity of one of the studies (Aronson *et al.*) was limited by the lack of general-population controls. NAS found that the other study (Demers *et al.*) was well conducted and appears to have used appropriate statistical methods. NAS also noted, however, that PCB congeners also have non-dioxin-like components, and that the observed effects may be attributable to those components.

Another study found further evidence of increased breast cancer risk associated with increased serum TCDD. (Warner M, Eskenazi B, Mocarelli P, Gerthoux PM, Samuels S, Needham L, Patterson D, Brambilla P. Serum dioxin concentrations and breast cancer risk in the Seveso Women's Health Study. *Environmental Health Perspectives* 2002; 110(7) 625–628) NAS found that this study adjusted for risk factors and was apparently free from potential bias. NAS also noted, however, that the findings were potentially limited because they were based on only 15 cases.

In a Vietnam veteran study that included 4,140 female Vietnam veterans and 4,140 veteran controls that did not service in Vietnam, it was concluded that Vietnam veterans did not experience a significantly higher prevalence of breast cancer. (Kang HK, Mahan CM, Lee KY, Magee CA, Selvin S. 2000. Prevalence of gynecologic cancers among female Vietnam veterans. *Journal of Occupational & Environmental Medicine* 42(11):1121–1127.) Although the prevalence of breast cancer was higher in female Vietnam veterans than in non-Vietnam veterans, the difference was not considered statistically significant. This study, also, was considered by NAS to be well designed, have adequate power, and be highly relevant for the assessment of the effect of Agent Orange and other herbicides on breast cancer risk in Vietnam veterans. NAS also noted, however, that the study's usefulness may be limited because questions on exposure focused on the Vietnam experience as a whole instead of on exposures to Agent Orange, other herbicides or their contaminants.

NAS concluded that there is still inadequate or insufficient evidence to determine whether there is an association between exposure to herbicides and breast cancer.

As noted above, studies reviewed in prior NAS reports predominately showed no association between breast cancer and herbicide exposure, or possibly a limited protective association. The additional evidence reviewed in Update 2002 includes evidence consistent with those prior studies, as well as some studies providing evidence of an association, subject to the limitations discussed above.

Taking account of the available evidence and NAS's analysis, the Secretary has found that the credible evidence against an association between herbicide exposure and breast cancer outweighs the credible evidence for such an association, and he has determined that a positive association does not exist.

Cancers of the Female Reproductive System

NAS noted that the cancers of the female reproductive system include cancers of the cervix, endometrium (also referred to as the corpus uteri), and ovaries. Cervical cancers occur more often in African-American women than in white women, whereas white women are more likely to develop endometrial and ovarian cancers. The incidence of endometrial and ovarian cancer also depends on age, with older women at greater risk. Human papillomavirus infection is the most important risk factor for cervical cancer. Diet, a family history of the disease, and breast cancer are among the risk factors for endometrial and ovarian cancers. NAS noted in VAO and subsequent reports that there is inadequate or insufficient information to determine whether an association exists between exposure to herbicides and cancers of the female reproductive system.

In Update 2002, NAS reported that the environmental study involving Chapaevsk, Russia (Revich *et al.*, 2001) appeared to show an increased risk of cervical cancer, but noted that the number of cases on which the rates were calculated was not provided and may have been small, and further noted that the potential for confounding by socioeconomic factors was not addressed.

NAS noted that the Kang *et al.* (2000) environmental study on gynecologic cancers among female Vietnam veterans provided some evidence that service in Vietnam does not substantially increase the risk of uterine, ovarian or cervical cancer, but the report made no attempt to examine exposures to herbicides or TCDD in Vietnam.

NAS found that no strong studies addressing female reproductive cancers