

NAS in Update 2002. Both studies (Burns *et al.*, 2001; Thorn *et al.*, 2000) demonstrated no excess mortality from brain cancer. NAS noted, however, that both studies were small and had limited power to detect an increase in an uncommon outcome.

NAS concluded that there was no new evidence to change the previous determination that there is limited or suggestive evidence of no association between exposure to herbicides and brain tumors.

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

AL Amyloidosis

Amyloidosis refers to a group of diseases in which insoluble fibrillar proteins (amyloid) accumulate in tissues to a point that causes organs to malfunction. NAS reviewed AL amyloidosis (also sometimes referred to as primary amyloidosis), in which the light chain of immunoglobulin molecules is the aberrant protein. AL amyloidosis is the most common form of amyloidosis in the United States.

NAS in Update 2000 found there was inadequate or insufficient information to determine whether an association exists between exposure to herbicides and AL amyloidosis.

No relevant occupational, environmental, or Vietnam-veteran studies have been published since Update 2000.

NAS concluded that there is no information to change the conclusion that there is inadequate or insufficient evidence to determine whether an association exists between exposure to herbicides and AL amyloidosis.

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

Endometriosis

NAS reviewed endometriosis for the first time in Update 2002.

Endometrium is the tissue that lines the inside of the uterus. In endometriosis, endometrium is found outside the uterus, usually in other parts of the reproductive system, the abdomen, or the tissues near the

reproductive organs, and results in inflammation, internal bleeding, and degeneration of blood and tissue which can cause scarring, pain, infertility, adhesions, and intestinal problems. The cause of endometriosis is unknown.

Suspicion that TCDD is involved in the etiology of endometriosis began after the observation that the incidence of endometriosis was higher in monkeys treated with low doses of TCDD than in control monkeys.

In Update 2002, NAS reviewed a study which analyzed blood TCDD concentrations in 79 women who were being evaluated for infertility, 44 of whom were diagnosed with endometriosis by laparoscopy. (Mayani A, Barel S, Soback S, and Almagor M. 1997. Dioxin concentration in women with endometriosis. *Human Reproduction*. 12:373–375.) Eight of the 44 women with endometriosis were positive for TCDD compared with one of the 35 controls. NAS noted that the number of subjects in this study is small, the ethnic distribution differed, and the limit of TCDD detection was not clear. Although the study reported an increased risk, the confidence interval was very wide and the finding was not statistically significant.

Another study assessed whether TCDD toxic equivalents (TEQs) in serum are associated with endometriosis in an infertile population of women who enrolled in fertility treatment. (Pauwels A, Schepens PJ, D'Hooghe T, Delbeke L, Dhont M, Brouwer A, Weyler J. 2001. The risk of endometriosis and exposure to dioxins and polychlorinated biphenyls: A case-control study of infertile women. *Human Reproduction*. 16:2050–5.) The case-control study evaluated 42 women with endometriosis and 27 controls without endometriosis, but with infertility related to other causes. The authors reported no association between median total TEQs and endometriosis in infertile women.

NAS concluded that there is inadequate or insufficient evidence to determine whether an association exists between exposure to herbicides and endometriosis.

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

Thyroid Homeostasis

NAS reviewed the thyrotoxic potential of herbicides for the first time in Update 2002.

The thyroid gland secretes hormones (T4 and T3) which stimulate metabolic rate. Secretion of T4 and T3 is under the control of thyroid-stimulating hormone (TSH), which is secreted by the anterior pituitary gland. The thyroid also secretes calcitonin, a hormone that controls calcium concentration in the blood and storage of calcium in bones. Chemical-induced alterations in thyroid homeostasis can adversely affect the development of many organ systems, including the nervous and reproductive systems. Most adverse effects are caused by lack of thyroid hormone alone rather than by increases in TSH. TCDD affects the concentrations of thyroid hormones; the effects appear to be species-dependent and may reflect both the dose and the duration of exposure. TCDD influences the metabolism of thyroid hormones and TSH. Studies of environmental exposure have emphasized thyroid alterations in prenatal and early childhood development rather than in adults.

One environmental study reviewed by NAS evaluated 38 mother-infant pairs, selected for normal birth weight and no complications. (Pluim HJ, Koppe JG, Olie K, Vd Slikke JW, Kok JH, Vulsma T, Van Tijn D, De Vijlder JJ. 1992. Effects of dioxins on thyroid function in newborn babies. *Lancet*. 339:1303.) In cord blood, the concentrations of total T4 and thyroxine-binding globulin (TBG) were suggestively higher in the high exposure group, but no other measurements approached significance. At 1 week, total T4 and the ratio of total T4 to TBG were significantly greater in the high-exposure than the low-exposure group, and the same was true at 11 weeks. TSH concentrations were also significantly higher at 11 weeks. When only infants who were breastfed for the full 11 weeks were considered, only the ratio of total T4 to TBG remained significantly different. In a subset of the births for which values were obtained in both the cord and 1-week samples, the increases in total T4 and in TBG were substantially higher in the high-exposure group. NAS stated that concerns about those results are related to the size of the study sample and the loss of nearly one-fourth of the maternal-blood samples and five of the cord-blood samples for all thyroid measurements. Several more samples were insufficient for some of the analyses.

A larger study of 105 mother-infant pairs conducted similar analyses. (Koopman-Esseboom C, Morse DC, Weisglas-Kuperus N, Lutkeschipholt IJ, Van der Paauw CG, Tuinstra LG, Brouwer A, Sauer PJ. 1994. Effects of dioxins and polychlorinated biphenyls