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NASDAQ/NMS will be more beneficial to its stockholders than the present listing on the Amex because:

(1) The Company believes that the NASDAQ/NMS system of competing market-makers will result in increased visibility and sponsorship for the Common Stock than is presently the case with the single specialist assigned to the stock on the Amex;

(2) The Company believes that the NASDAQ/NMS system will offer the Company's stockholders more liquidity than is presently available on the Amex and less volatility in quoted prices per share when trading volume is slight;

(3) The Company believes that the NASDAQ/NMS system will offer the opportunity for the Company to secure its own group of market-makers and, in doing so, expand the capital base available for trading in its Common Stock; and

(4) The Company believes that firms making a market in the Company's Common Stock on the NASDAQ/NMS system will be inclined to issue research reports concerning the Company, thereby increasing the number of firms providing institutional research and advisory reports.

Any interested person may, on or before January 20, 1994, submit by letter to the Secretary of the Securities and Exchange Commission, 450 Fifth Street, NW., Washington, DC 20549, facts bearing upon whether the application has been made in accordance with the rules of the exchanges and what terms, if any, should be imposed by the Commission for the protection of investors. The Commission, based on the information submitted to it, will issue an order granting the application after the date mentioned above, unless the Commission determines to order a hearing on the matter.

For the Commission, by the Division of Market Regulation, pursuant to delegated authority.

Jonathan G. Katz,

Secretary.

[FR Doc. 94-50 Filed 1-3-94; 8:45 am]

BILLING CODE 8010-01-M

TENNESSEE VALLEY AUTHORITY

Paperwork Reduction Act of 1980, As Amended by Public Law 99-591; Information Collection Under Review by the Office of Management and Budget (OMB)

AGENCY: Tennessee Valley Authority.

ACTION: Information collections under review by the Office of Management and Budget (OMB).

SUMMARY: The Tennessee Valley Authority (TVA) has sent to OMB the following proposal for the collection of information under the provisions of the Paperwork Reduction Act of 1980 (44 U.S.C. chapter 35), as amended by Public Law 99-591.

Requests for information, including copies of the information collection proposed and supporting documentation, should be directed to the Agency Clearance Officer whose name, address, and telephone number appear below. Questions or comments should be made within 30 days directly to the Agency Clearance Officer and also to the Desk Officer for the Tennessee Valley Authority, Office of Information and Regulatory Affairs, Office of Management and Budget, Washington, DC 20503; Telephone: (202) 395-3084.

Agency Clearance Officer: Mark R. Winter, Tennessee Valley Authority, 1101 Market Street (BR 6B), Chattanooga, TN 37402-2801; (615) 751-2523.

Type of Request: Regular submission.

Title of Information Collection: TVA Aquatic Plant Management.

Frequency of Use: On occasion.

Type of Affected Public: Individuals or households.

Small Businesses or Organization Affected: No.

Federal Budget Functional Category Code: 452.

Estimated Number of Annual Responses: 2,000.

Estimated Total Annual Burden Hours: 400.

Estimated Average Burden Hours Per Response: .2.

Need For and Use of Information: TVA committed to involving the public in developing plans for managing aquatic plants in individual TVA lakes under a Supplemental Environmental Impact Statement completed in August 1993. This proposed survey will provide a mechanism for obtaining input into this planning process from a representative sample of people living near each lake. The information obtained from the survey will be factored into the development of aquatic plant management plans for Chickamauga, Kentucky, Wheeler, Nickajack and Guntersville Lakes.

John J. O'Donnell,

Vice President, Facilities Services.

[FR Doc. 94-12 Filed 1-3-94; 8:45 am]

BILLING CODE 8120-08-M

DEPARTMENT OF VETERANS AFFAIRS

Disease Not Associated With Exposure to Certain Herbicide Agents

AGENCY: Department of Veterans Affairs.

ACTION: Notice.

SUMMARY: As required by law, the Department of Veterans Affairs (VA) hereby gives notice that the Secretary of Veterans Affairs, under the authority granted by the Agent Orange Act of 1991, has determined that a presumption of service connection based on exposure to herbicides used in the Republic of Vietnam during the Vietnam era is not warranted for the following conditions: Prostate cancer, peripheral neuropathy, hepatobiliary cancers, bone cancers, female reproductive cancers, renal cancers, testicular cancer, leukemia, abnormal sperm parameters and infertility, cognitive and neuropsychiatric disorders, motor/coordination dysfunction, metabolic and digestive disorders, immune system disorders, circulatory disorders, respiratory disorders (other than lung cancer), nasal/nasopharyngeal cancer, skin cancer, gastrointestinal tumors, bladder cancer, brain tumors, and any other condition for which the Secretary has not specifically determined a presumption of service connection is warranted.

FOR FURTHER INFORMATION CONTACT: John Bisset, Jr., Consultant, Regulations Staff, Compensation and Pension Service, Veterans Benefits Administration, Department of Veterans Affairs, 810 Vermont Avenue, NW., Washington, DC 20420, (202) 233-3005.

SUPPLEMENTARY INFORMATION: Section 3 of the Agent Orange Act of 1991, Public Law 102-4, 105 Stat. 11 (1991), directed the Secretary to enter into an agreement with the National Academy of Sciences (NAS) to review the scientific evidence concerning the association between exposure to herbicides used in support of military operations in the Republic of Vietnam during the Vietnam era and each disease suspected to be associated with such exposure. Congress mandated that NAS determine, to the extent possible, (1) whether there is a statistical association between the suspect diseases and herbicide exposure, taking into account the strength of the scientific evidence and the appropriateness of the methods used to detect the association; (2) the increased risk of disease among individuals exposed to herbicides during service in the Republic of Vietnam during the Vietnam era; and (3)

whether there is a plausible biological mechanism or other evidence of a causal relationship between herbicide exposure and the suspect disease.

Section 2 of Public Law 102–4 provides that whenever the Secretary determines, based on sound medical and scientific evidence, that a positive association (i.e., the credible evidence for the association is equal to or outweighs the credible evidence against the association) exists between exposure of humans to an herbicide agent (i.e., a chemical in an herbicide used in support of the United States and allied military operations in the Republic of Vietnam during the Vietnam era) and a disease, the Secretary will publish regulations establishing presumptive service connection for that disease. If the Secretary determines that a presumption of service connection is not warranted, he will publish a notice of that determination, which includes an explanation of the scientific basis for that determination.

Although Public Law 102–4 does not define "credible", it does instruct the Secretary to "take into consideration whether the results are 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, etc., some studies are clearly more credible than others, and the Secretary has given them more weight in evaluating the overall credibility of the evidence concerning specific diseases.

After reviewing approximately 6,420 abstracts of scientific or medical articles and selecting approximately 230 epidemiologic studies for detailed analysis, consulting with outside experts, and conducting public hearings, NAS issued a report, entitled "Veterans and Agent Orange: Health Effects of Herbicides Used in Vietnam", on July 27, 1993. The Secretary announced that same day that he had concluded that a positive association exists between exposure to herbicides used in the Republic of Vietnam and the subsequent development of Hodgkin's disease and porphyria cutanea tarda. Proposed regulations were published in the Federal Register on September 28, 1993 (See 58 FR 50528–30). The Secretary also announced that VA would review the remaining findings in the NAS report to determine whether a positive association exists between herbicide exposure and any other conditions. That review has been completed and this notice, pursuant to Public Law 102–4, conveys the Secretary's determination that there is no positive association between herbicide exposure and prostate cancer, peripheral neuropathy, hepatobiliary cancers, bone cancers, female reproductive cancers, renal cancers, testicular cancer, leukemia, abnormal sperm parameters and infertility, cognitive and neuropsychiatric disorders, motor/coordination dysfunction, metabolic and digestive disorders, immune system disorders, circulatory disorders, respiratory disorders (other than lung cancer), nasal/nasopharyngeal cancer, skin cancer, gastrointestinal tumors, bladder cancer, brain tumors, and any other condition for which the Secretary has not specifically determined a presumption of service connection is warranted.

The NAS report assigns prostate cancer to a category labeled limited/suggestive evidence of an association, which it defined as meaning there is evidence suggestive of an association between herbicide exposure and a particular health outcome, but that evidence is limited because chance, bias, and confounding could not be ruled out with confidence. Prostate cancer is a very common male genitourinary cancer which shows marked increased prevalence with age. There are statistically significant occupational studies which show no association between prostate cancer and herbicide exposure (e.g., Fingerhut M.A., Halperin W.E., Marlow D.A., Piacitelli L.A., Honchar P.A., Sweeney M.H., Greife A.L., Dill P.A., Steenland K., Suruda A.J. 1991. Cancer mortality in workers exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin. New England Journal of Medicine 324:212–218; Manz A., Berger J., Dwyer J.H., Flesch-Janys D., Nagel S., Waltsgott H. 1991. Cancer mortality among workers in chemical plant contaminated with dioxin. Lancet 338:959–964; Saracci R., Kogevinas M., Bertazzi P.A., Bueno De Mesquita B.H., Coggon D., Green L.M., Kauppinen T., L'Abbe K.A., Littorin M., Lynge E., Mathews J.D., Neuberger M., Osman J., Pearce N., Winkelman R. 1991. Cancer mortality in workers exposed to chlorophenoxy herbicides and chlorophenols. Lancet 338:1027–1032). Some occupational studies have shown a slight elevated risk for prostate cancer among farm and forestry workers (e.g., Burmeister L.F., 1981. Cancer mortality in Iowa farmers: 1971–1978. Journal of the National Cancer Institute 66:461–464; Alavanja M.C., Merkle S., Teske J. Eaton B., Reed B. 1989. Mortality among forest and soil conservationists. Archives of Environmental Health 44:94–101); however, only one study concerning a small sub-set of farmers (Morrison H., Savitz, D., Semenciw R., Hulka B., Mao Y., Morison D., Wigle D. 1993. Farming and prostate cancer mortality. American Journal of Epidemiology 137:270–280) associated the increased risk of prostate cancer among farmers specifically with herbicide exposure. The Morrison study is so recent that it it too early to determine whether its results will be replicated by other research. Accordingly, the Secretary has found that the credible evidence against an association between prostate cancer and herbicide exposure outweighs the credible evidence for such an association, and he has determined that a positive association does not exist.

The NAS report assigns peripheral neuropathy, hepatobiliary cancers, bone cancers, female reproductive cancers, renal cancers, testicular cancer, leukemia, abnormal sperm parameters and infertility, cognitive and neuropsychiatric disorders, motor/coordination dysfunction, metabolic and digestive disorders, immune system disorders, circulatory disorders, respiratory disorders (other than lung cancer), and nasal/nasopharyngeal cancer to a category labeled inadequate/insufficient evidence to determine whether an association exists, which is defined as meaning that the available studies are of insufficient quality, consistency, or statistical strength to permit a conclusion regarding the presence or absence of an association with herbicide exposure.

Peripheral neuropathy can be induced by many common medical and environmental disorders unrelated to herbicide exposure, such as aging, alcoholism, diabetes, and exposure to other toxic chemicals. The last time VA considered this issue, it determined, after receiving the advice of the Veterans' Advisory Committee on Environmental Hazards, that there was sufficient evidence to meet the requirements for a "significant statistical association," the standard in effect at that time, between exposure to herbicides containing dioxin and the subsequent development of peripheral neuropathy under certain circumstances (See 57 FR 2236–38). That conclusion, however, relied heavily on case reports.

which are anecdotal and have no statistical significant, and occupational studies such as Singer and colleagues (1982) (Singer R., Moses M., Valciukas J., Lilis R., Selikoff I.J., 1982. Nerve conduction velocity studies of workers employed in the manufacture of phenoxy herbicides. Environmental Research 29:297–311) whose credibility is compromised because they did not apply consistent methods to define a comparison group, determine exposure, evaluate clinical deficits, use standard definitions of peripheral neuropathy, or eliminate confounding variables. The Singer study, for example, excluded individuals with excessive alcohol consumption from the controls but not from the subjects of the study. Other occupational studies, such as Suskind and Herzberg (1984) (Suskind R.R., Hertzberg V.S., 1984. Human health effects of 2,4,5–T and its toxic contaminants. Journal of the American Medical Association 251:2372–2380), which did not have those methodological problems, showed no difference in the incidence of peripheral neuropathy for workers exposed to herbicides and workers not so exposed. Accordingly, the Secretary has found that the credible evidence against an association between peripheral neuropathy and herbicide exposure outweighs the credible evidence for such an association, and he has determined that a positive association does not exist.

Hepatobiliary cancers are cancers of the liver and bile duct. There are a variety of risk factors that should be considered by a credible study, including hepatitis B and C, alcohol abuse, cirrhosis, exposure to polychlorinated biphenyl (PCB), and smoking. The relevant studies are few, and have not adequately controlled for these risk factors. A Swedish case control study (Hardell L., Bengtsson N.O., Jonsson U., Eriksson S., Larsson L.G., 1984. Aetiological aspects on primary liver cancer with special regard to alcohol, organic solvents and acute intermittent porphyria: an epidemiological investigation. British Journal of Cancer 50:389–397) showed a relationship between herbicide exposure and the subsequent development of hepatobiliary cancer however, other studies of similar size (Ronco G, Costa G., Lynge E., 1992. Cancer risk among Danish and Italian farmers. British Journal of Industrial Medicine 49:220–225; Wiklund K., 1983. Swedish agricultural workers: a group with a decreased risk of cancer. Cancer 51:566–568) indicated no relationship. A large occupational study (Fingerhut et al., 1991) and a study of farmers in Denmark and Italy (Ronco et al., 1992) found no relationship. Accordingly, the Secretary has found that the credible evidence against an association between hepatobiliary cancer and herbicide exposure outweighs the credible evidence for such an association, and he has determined that a positive association does not exist.

Bone cancers were considered together with joint cancers by NAS. Because of the rarity of bone cancers, most studies have been too small to detect a significant risk. There has not been a consistent finding of bone cancer in exposed groups; the preponderance of studies show no association, and the few studies that demonstrate a positive relationship (Fingerhut et al., 1991; Breslin P., Kang H., Lee y., Burt V., Shepard B.M., 1988. Proportionate mortality study of U.S. Army and U.S. Marine Corps veterans of the Vietnam War. Journal of Occupational Medicine 30:412–419) are small and have large confidence intervals which include one. The small size of the studies and the confidence limitations compromise their significance. Accordingly, the Secretary has found that the credible evidence against an association between bone cancers and herbicide exposure outweighs the credible evidence for such an association, and he has determined that a positive association does not exist.

Female reproductive cancers reviewed by NAS include those of the breast, uterus, cervix, ovary, and other genital malignancies. The data related to women and herbicide exposure is extremely limited because few of the studies included women. A large number of the breast cancer studies showed no association. Two studies (Thomas T.L., Kang H., Dalager N., 1991. Mortality among women Vietnam veterans, 1973–1987. American Journal of Epidemiology 134:973–980; Manz et al., 1991) showed an increased risk for breast cancer which was not significant since both studies failed to control for reproductive histories and had methodological problems. Only one small case control study (Donna A., Betta P–G., Robutti F., Crosignani P., Berrino F., Bellingeri D., 1984. Ovarian mesothelial tumors and herbicides: a case control study. Carcinogenesis 5:941–942) showed an association with ovarian cancer, but the confidence intervals were very wide. The larger occupational and farm worker studies all showed significantly lower mortality ratios than expected. Likewise, studies of exposures generally found less uterine and cervical cancer than expected. Accordingly, the Secretary has found that the credible evidence against an association between female reproductive cancers and herbicide exposure outweighs the credible evidence for such an association, and he has determined that a positive association does not exist.

The leather industry, asbestos, cadmium, petroleum products, analgesics, smoking, and obesity have been associated with renal cancers. Studies of renal cancer have generally produced inconclusive results, in some cases because of failure to adequately control for these confounding factors. Only one study of agricultural and forest workers (Alavanja et al., 1989) showed a significantly increased risk of death from renal cancers; however, the preponderance of studies, including the two largest (Wiklund, 1983; Burmeister, 1981), showed either no relationship with renal cancers or increased risk which was not significant. Accordingly, the Secretary has found that the credible evidence against an association between renal cancers and herbicide exposure outweighs the credible evidence for such an association, and he has determined that a positive association does not exist.

Major risk factors for testicular cancer are undescended testis and other factors, such as genetic abnormalities, infections, etc., which produce atrophy and dysfunction. In general, occupational studies (Ronco et al., 1992; Wiklund, 1983) have shown no association between herbicide exposure and testicular cancer. Occupational and environmental studies have found either no association or increased risk which was not significant. Studies concerning Vietnam veterans were inconsistent, and in those that found increased risk, that risk was generally not significant. Accordingly, the Secretary has found that the credible evidence against an association between testicular cancer and herbicide exposure outweighs the credible evidence for such an association, and he has determined that a positive association does not exist.

Potential evidence for an association between herbicide exposure and leukemia comes primarily from studies of farmers (Ronco et al., 1992; Wigle D.T., Semenciw R.B., Wilkins K., Riedel D., Ritter L., Morrison H.I., Mao Y., 1990. Mortality study of Canadian male farm operators: non-Hodgkin's lymphoma mortality and agricultural practices in Saskatchewan. Journal of the National Cancer Institute 82:575–582) and residents of Seveso, Italy (Bertazzi P.A., Zocchetti C., Pesatori A.C., Guercilena S., Sanarico M., Radice L., 1989b. Ten-year mortality study of

the population involved in the Seveso incident in 1976. American Journal of Epidemiology 129:1187–1200; Bertazzi P.A., Zocchetti C., Pesatori A.C., Guercilena S., Consonni D., Tironi A., Landi M.T., 1992. Mortality of a young population after accidental exposure to 2,3,7,8-tetrachlorodibenzodioxin. International Journal of Epidemiology 21:118–123). The studies of farmers did not control for other confounding exposures (Brownson R.C., Reif J.S., Chang J.C., Davis J.R., 1989. Cancer risk among Missouri farmers. Cancer 64:2381–2385.; Brown L.M., Blair A., Gibson R., Everett G.D., Cantor K.P., Schuman L.M., Burmeister L.F., Van Lier S.F., Dick F. 1990. Pesticide exposures and other agricultural risk factors for leukemia among men in Iowa and Minnesota. Cancer Research 50:6585–6591). When farmers were stratified by suspected herbicide exposure, the incidence of leukemia was generally not elevated. Any elevation appeared to be due to factors other than herbicide exposure, e.g., risk was higher among chicken farmers than wheat farmers (Alavanja M.C., Blair A, Merkle S., Teske J. Eaton B., 1988. Mortality among agricultural extension agents. American Journal of Industrial Medicine 14:167–176). The suggestive evidence of increased risk concerning Seveso, Italy was not significant because of the small number of actual cases in which leukemia was found. Since none of the studies demonstrated a dose-response for any subtype of leukemia, it is not possible to attribute leukemia to herbicide exposure. Accordingly, the Secretary has found that the credible evidence against an association between leukemia and herbicide exposure outweighs the credible evidence for such an association, and he has determined that a positive association does not exist.

The common parameters used to evaluate toxic effects to sperm are number, motility, structure, and morphology. Many chemicals have been implicated in interfering with motility and sperm structure (Wyrobek A.J., Gordon L.A., Burkhart J.G., Francis M.W., Kapp R.W., Letz G., Malling H.V., Topham J.C., Whorton M.D., 1983. An evaluation of human sperm as indicators of chemically induced alterations of spermatogenic function. A report of the U.S. Environmental Protection Agency Gene-Tox Program. Mutation Research 115:73–148). One occupational study (Lerda D., Rizzi R., 1991. Study of reproductive function in persons occupationally exposed to 2,4-dichlorophenoxyacetic acid (2,4–D). Mutation Research 262:47–50) and one study of Vietnam veterans (Air Force Health Study (AFHS), 1992. An Epidemiologic Investigation of Health Effects in Air Force Personnel Following Exposure to Herbicides. Reproductive Outcomes. Brooks AFB: USAF School of Aerospace Medicine. AL–TR–992–0900 602 pp.) found no association with decreased sperm count. Another study of Vietnam veterans (Centers for Disease Control (CDC), 1989. Comparison of Serum Levels of 2,3,7,8-Tetrachlorodibenzo-p-dioxin with Indirect Estimates of Agent Orange Exposure Among Vietnam Veterans: Final Report. Atlanta: U.S. Department of Health and Human Services) found lower sperm concentration and reduced sperm motility, but suggested these outcomes may be associated with the Vietnam experience rather than exposure to herbicides. Infertility usually incorporates two concepts: the inability to conceive and the inability to produce live children. Most studies do not take into account the desire for children, contraceptive practices, and other factors influencing fertility. NAS found no occupational or environmental studies examining herbicide exposure and infertility, and veteran studies (Field B., Kerr C., 1988. Reproductive behavior and consistent patterns of abnormality in offspring of Vietnam veterans. Journal of Medical Genetics 25:819–826; AFHS, 1992; Centers for Disease Control (CDC), 1988. Health status of Vietnam veterans. III. Reproductive outcomes and child health. Journal of the American Medical Association 259:2715–2717) do not support an association between herbicide exposure and infertility. Accordingly, the Secretary has found that the credible evidence against an association between abnormal sperm parameters and infertility and herbicide exposure outweighs the credible evidence for such an association, and he has determined that a positive association does not exist.

Studies of cognitive and neuropsychiatric disorders are beset by a number of methodologic problems, including exposure measures, the wide variety of "standardized" test instruments used, and the inability to detect or correct for other influences on test results such as emotional state, non-neurologic disease, metabolic conditions, fatigue, medications, or style of the examiner. Because of their failure to adequately control for these confounding factors, these studies lack credibility in assessing the relationship of herbicide exposure to these conditions. Accordingly, the Secretary has found that there is no credible evidence for an association between cognitive and neuropsychiatric disorders and herbicide exposure, and he has determined that a positive association does not exist.

There were no significant studies available to analyze whether an association exists between herbicide exposure and motor/coordination dysfunction. Accordingly, the Secretary has found that there is no credible evidence for an association between motor/coordination dysfunction and herbicide exposure, and he has determined that a positive association does not exist.

Metabolic and digestive disorders (diabetes mellitus, hepatic enzyme abnormality, lipid abnormalities, and ulcers) were also categorized by NAS as health outcomes with inadequate/insufficient evidence to determine whether an association exists. Although NAS found no biologic basis to suspect an association between herbicide exposure and diabetes, abnormal glucose tolerance tests have been reported in three studies (Sweeney M.H., Fingerhut M.A., Arezzo J.C., Hornung R.W., Connally L.B. In press. Peripheral neuropathy after occupational exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD).; Air Force Health Study. 1991. An Epidemiologic Investigation of Health Effects in Air Force Personnel Following Exposure to Herbicides. Serum Dioxin Analysis of 1987 Examination Results. Brooks AFB, TX: USAF School of Aerospace Medicine. 9 vols.; Pazderova-Vejlupkova J., Lukas E., Nemcova M., Pickova J., Jirasek L., 1991. The development and prognosis of chronic intoxication by tetrachlorodibenzo-p-dioxin in men. Archives of Environmental Health 38:5–11). While this suggests such an association, the evidence is inconclusive and its credibility is questionable because an abnormal glucose tolerance test is not an absolute indicator of diabetes and none of these studies allowed for the confounding role of obesity. Two other studies found no association (Moses M., Lilis R., Crow K.D., Thornton J., Fischbein A., Anderson H.A., Selikoff I.J., 1984. Health status of workers with past exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin in the manufacture of 2,4,5-trichlorophenoxyacetic acid: Comparison of findings with and without chloracne. American Journal of Industrial Medicine 5:161–182; Suskind and Hertzberg, 1984), and a number of studies have shown no increased death rates from diabetes (Bertazzi et al., 1989; Cook R.R., Bond G.G., Olson R.A., Ott M.G., 1987. Update of the mortality

experience of workers exposed to chlorinated dioxins. Chemosphere 16:2111–2116; Henneberger P.K., Ferris B.G. Jr., Monson R.R., 1989. Mortality among pulp and paper workers in Berlin, New Hampshire. British Journal of Industrial Medicine 46:658–664). Accordingly, the Secretary has found that the credible evidence against an association between diabetes and herbicide exposure outweighs the credible evidence for such an association, and he has determined that a positive associations does not exist.

The studies related to hepatic enzyme abnormality did not demonstrate an association with liver disease, and confounding factors (alcohol abuse, cirrhosis, hepatitis, and other toxic chemicals) were not ruled out. Studies showing lipid abnormalities do not control for the confounding variables of obesity and genetic factors, and no medical significance of the modest and variable increases has been demonstrated. The risk of gastric ulcers in exposed populations has not been sufficiently studied to establish an association with herbicide exposure. Only one study (Suskind and Hertzberg, 1984) indicates any increase, and in that study it is difficult to rule out the many factors (e.g., alcoholism, non-steroidal anti-inflammatory drugs, and H. pylori infection) known to be associated with ulcers. Accordingly, the Secretary has found that there is no credible evidence for an association between metabolic and digestive disorders (other than diabetes) and herbicide exposure, and he has determined that a positive association does not exist.

The available data deal with two categories of immune system disorders: immune modulation and autoimmunity. Many immune parameters have been studied; however, few show a relationship to herbicide exposure. Most studies address such a wide range of immune parameters that it is likely that at least some of the positive results are due to chance alone, which undermines the credibility of those studies. Furthermore, the clinical meaning, i.e., the relationship of immune disorders to disease, is unclear. Other studies (e.g., Pocchiari F., Silano V., Zampieri A., 1979. Human health effects from accidental release of tetrachlorodibenzo-p-dioxin (TCDD) at Seveso, Italy. Annals of the New York Academy of Sciences 320:311–320; Gbezzi I., Cannatelli P., Assennato G., Merlo F., Mocarelli P., Brambilla P., Sicurello F., 1982. Potential 2,3,7,8-tetrachlorodibenzo-p-dioxin exposure of Seveso decontamination workers. A controlled prospective study. Scandinavian Journal of Work, Environment, and Health 8:176–179) found no relationship between immune system disorders and herbicide exposure. Accordingly, the Secretary has found that the credible evidence against an association between immune system disorders and herbicide exposure outweighs the credible evidence for such an association, and he has determined that a positive association does not exist.

Most occupational studies concerning circulatory disorders (e.g., Moses et al., 1984; Suskind and Hertzberg, 1984) showed no increased mortality or morbidity from circulatory disorders after herbicide exposure. The studies of the residents of Seveso, Italy (Bertazzi, P.A., Zocchetti C., Pesatori A.C., Guercilena S., Sanarico M., Radice L., 1989a. Mortality in an area contaminated by TCDD following an industrial incident. Medicina Del Lavoro 80:316–329; Bertazzi et al., 1989b) showed some increased risk of mortality in the first five year follow-up; however, these studies had a number of technical problems: they were not specific to circulatory disease and did not control for the confounding variables of smoking, diabetes, and hypertension. Veteran studies (e.g., CDC, 1988) have suggested that any increase in heart disease may be associated with the Vietnam experience rather than herbicide exposure, and most of these studies did not adjust for confounding variables. Accordingly, the Secretary has found that the credible evidence against an association between circulatory diseases and herbicide exposure outweighs the credible evidence for such an association, and he has determined that a positive association does not exist.

NAS examined studies that covered a wide variety of respiratory disorders (e.g., chronic bronchitis, asthma, pleurisy, pneumonia, and tuberculosis), other than respiratory cancer. Studies of individuals exposed in occupational settings revealed no increase in mortality from respiratory disease (Coggon D., Pannett B., Winter P., 1991. Mortality and incidence of cancer at four factories making phenoxy herbicides. British Journal of Industrial Medicine 48:173–178; Blair A., 1983. Lung cancer and other causes of death among licensed pesticide applicators. Journal of the National Cancer Institute 71:31–37; Alavanja et al., 1989; Coggon D., Pannett B., Winter P.D., Acheson E.D., Bonsall J., 1986. Mortality of workers exposed to 2-methyl—chlorophenoxyacetic acid. Scandinavian Journal of Work, Environment, and Health 12:448–454). Environmental exposure studies similarly showed no significant differences in mortality due to respiratory disease (Bertazzi et al., 1989a,b). Also, mortality studies of Vietnam veterans generally found no increased risk.

Morbidity data are generally difficult to evaluate because of methodological problems and because studies focused on symptoms, lung function tests and x-ray interpretation rather than disease (e.g., Calvert et al., 1991; Pollei S., Mettler F.A. Jr., Kelsey C.A., Walters M.R., White R.E., 1986. Follow-up chest radiographs in Vietnam veterans: Are they useful? Radiology 161:101–102). One occupational study (Calvert G.M., Sweeney M.H., Morris J.A., Fingerhut M.A., Hornung R.W., Halperin W.E., 1991. Evaluation of chronic bronchitis, chronic obstructive pulmonary disease, and ventilatory function among workers exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin. American Review of Respiratory Disease 144:1302–1306) showed no excess morbidity; another occupational study (Suskind and Hertzberg, 1984) found increased symptomatology of respiratory disease, but did not adequately control for the confounding factor of age. Accordingly, the Secretary has found that the credible evidence against an association between respiratory disorders and herbicide exposure outweighs the credible evidence for such an association, and he has determined that a positive association does not exist.

NAS noted an association between nasal cancers and occupational exposure to nickel and to chromates. Exposure to wood dust is also a risk factor for nasal cancers; smoking and exposure to formaldehyde may increase the risk associated with wood dust. There is also evidence that leather workers have an increased risk for nasal cancers, and that there is an association between chronic nasal diseases and consumption of salt-preserved foods. Most studies (e.g., Wiklund, 1983; Ronco et al., 1992) showed inconclusive results, and often did not control for confounding variables. Two other epidemiological studies based on the same three cases (Saracci et al., 1991; Coggon D., Pannett B., Winter P.D., Acheson E.D., Bonsall J., 1986. Mortality of workers exposed to 2 methyl-4-chlorophenoxyacetic acid. Scandinavian Journal of Work, Environment, and Health 12:448–454) and one case-control study (Hardell L., Johansson B., Axelson O., 1982. Epidemiological study of nasal and nasopharyngeal cancer and their relation to phenoxy acid or chlorophenol exposure. American Journal of Industrial Medicine 3:247–257) showed increased risk associated with herbicide exposure; however, that risk was not statistically

significant, which diminishes the importance of these studies. Accordingly, the Secretary has found that the credible evidence against an association between nasal/nasopharyngeal cancers and herbicide exposure outweighs the credible evidence for such an association, and he has determined that a positive association does not exist.

NAS also reviewed the literature with respect to possible associations between herbicide exposure and various reproductive effects, i.e., spontaneous abortion, birth defects, neonatal infant deaths and stillbirths, low birth weight, and childhood cancers in offspring. These reproductive effects were categorized by NAS as health outcomes with inadequate/insufficient evidence to determine whether an association exists because the studies were of inadequate statistical power for specific birth defects, contained a limited sample size, and/or failed to exclude bias and chance. It should be noted that to compensate a veteran for these conditions is beyond VA's authority (See title 38, U.S.C.) and would require enabling legislation.

NAS assigns four diseases or categories of diseases to a category labeled limited/suggestive evidence of no association with herbicide exposure which it defined as meaning that several adequate studies, covering the full range of levels of exposure that humans are known to encounter, are mutually consistent in not showing a positive association between herbicide exposure and the particular health outcome at any level of exposure. The conditions include skin cancer, gastrointestinal tumors (stomach cancer, pancreatic cancer, colon cancer, and rectal cancer), bladder cancer, and brain tumors. There were many credible studies (See NAS Report, Chapter 8) concerning all of these conditions that showed no association or a negative association with herbicide exposure. Accordingly, the Secretary has found that there is no credible evidence for an association between skin cancer, gastrointestinal tumors (stomach cancer, pancreatic cancer, colon cancer, and rectal cancer), bladder cancer, and brain tumors and herbicide exposure, and he has determined that a positive association does not exist.

NAS reviewed approximately 6,420 abstracts of scientific or medical articles as an integral part of the process that resulted in its report, entitled "Veterans and Agent Orange: Health Effects of Herbicides Used in Vietnam." From these articles, approximately 230 epidemiologic studies, including studies of people exposed to herbicides in occupational and environmental settings as well as studies of Vietnam veterans, were chosen for detailed review and analysis. In our judgment, the comprehensive review and evaluation of the available literature which NAS conducted in conjunction with its report has permitted us to identify all conditions for which the current body of knowledge supports a finding of an association with herbicide exposure. Accordingly, the Secretary has determined that there is no positive association between exposure to herbicides and any other condition for which he has not specifically determined that a presumption of service connection is warranted.

Dated: December 22, 1993.

Jesse Brown,

Secretary of Veterans Affairs.

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