a boltless track joint centered on a rail at the location of a flaw and being attached to the rail by two ''C'' clamps. It is claimed that avoidance of bolting the joint saves time, but more important, eliminates drilled bolt holes in the rail web which can serve later as sources of equally unwanted defects of a different type.

The petition requests that, for regions of the railroad where it is proposed to employ the device, the Federal Railroad Administration (FRA) specifically approve the following three conditions:

1. Once clamps are applied to detail fractures, engine burn fractures or defective welds measuring 25 percent or greater of the head area, train sped shall be limited to 60 miles per hour or the maximum allowable speed under section 213.9 of 49 CFR Part 213 for the class of track, whichever is lower.

2. BNSF shall remove these devices from the rails not more than 20 days after application. If the internal rail head defect has not been removed by that time, bolted joint bars will be immediately applied and the provisions of section 213.113 shall govern.

3. This waiver shall continue in effect for a period of 24 months from the date that it is issued by FRA.

It should be noted that this petition is the fourth in a series that commenced in August of 1990 (see at 55 FR 50266, 56 FR 13515 and 59 FR 9518 for earlier Federal Register notices descriptive of this program). In the virtual six years since that date, the device has been used, it is claimed, well over one hundred times and not once did a rail defect so protected progress to failure.

Interested parties are invited to participate in these proceedings by submitting written views, data or comments. FRA does to anticipate scheduling a public hearing in connection with these proceedings since the facts do not appear to warrant a hearing. If any interested party desires an opportunity for oral comment, they should notify EFRA, in writing, before the need of the comment period and specify the basis for their request.

All communications concerning these proceedings should identify the appropriate docket number (e.g., Waiver Petition Number RST–93–3) and must be submitted in triplicate to the Docket Clerk, Office of Chief Counsel, Federal Railroad Administration, 400 Seventh Street, SW., Washington, DC 20590. Communications received within 45 days after publication of this notice will be considered by FRA before final action is taken. Comments received after that date will be considered as far as practicable. All written communications concerning these proceedings are available for examination during regular business hours (9:00 a.m. to 5:00 p.m.) in Room 8201, 400 Seventh Street, SW., Washington, DC 20690.

Issued in Washington, DC on August 5, 1996.

Phil Olekszyk,

Acting Associate Administrator for Safety.

[FR Doc. 96–20262 Filed 8–7–96; 8:45 am]

BILLING CODE 4910–06–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: Hepatobiliary cancers, nasal/nasopharyngeal cancer, bone cancer, female reproductive cancers, breast cancer, renal cancer, testicular cancer, leukemia, abnormal sperm parameters and infertility, cognitive and neuropsychiatric disorders, motor/coordination dysfunction, chronic peripheral nervous system disorders, metabolic and digestive disorders, immune system disorders, circulatory disorders, respiratory disorders (other than certain respiratory cancers), 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, 810 Vermont Avenue, NW., Washington, DC 20420, telephone (202) 273–7230.

SUPPLEMENTARY INFORMATION: Section 3 of the Agent Orange Act of 1991, Pub. L. 102–4, 105 Stat. 11, directed the Secretary to seek to enter into an agreement with the National Academy of Sciences (NAS) to review and summarize 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 3 of Pub. L. 102–4 also required that NAS submit reports on its activities every two years (as measured from the date of the first report) for a ten-year period.

Section 2 of Pub. L. 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 is to publish a notice of that determination, including an explanation of the scientific basis for that determination. The Secretary's determination must be based on consideration of the NAS reports and all other sound medical and scientific information and analysis available to the Secretary.

Although Pub. L. 102–4 does not define ''credible,'' it does instruct the Secretary to ''take into consideration whether the results [of any study] 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, 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,'' 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 341–46).

NAS issued a second report, entitled ''Veterans and Agent Orange: Update 1996,'' on March 14, 1996. The focus of this updated review was on new scientific studies published since the release of the first report and updates of scientific studies previously reviewed.

The day that NAS issued its second report, the Secretary announced the formation of a VA task force to review the report and pertinent studies and to make recommendations to assist the Secretary in determining whether a positive association exists between herbicide exposure and any condition. That review has been completed, and the task force's recommendations were submitted to the Secretary. This notice, pursuant to Pub. L. 102–4, conveys the Secretary's determination that there is no positive association between herbicide exposure and hepatobiliary cancers, nasal/nasopharyngeal cancer, bone cancer, female reproductive cancers, breast cancer, renal cancer, testicular cancer, leukemia, abnormal sperm parameters and infertility, cognitive and neuropsychiatric disorders, motor/coordination dysfunction, chronic peripheral nervous system disorders, metabolic and digestive disorders, immune system disorders, circulatory disorders, respiratory disorders (other than certain respiratory cancers), 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.

NAS, in its 1996 report, assigns hepatobiliary cancers, nasal/nasopharyngeal cancer, bone cancer, female reproductive cancers, breast cancer, renal cancer, testicular cancer, leukemia, abnormal sperm parameters and infertility, cognitive and neuropsychiatric disorders, motor/coordination dysfunction, chronic peripheral nervous system disorders, metabolic and digestive disorders, immune system disorders, circulatory disorders, respiratory disorders (other than certain respiratory cancers), and skin cancer 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 strength to permit a conclusion regarding the presence or absence of an association with herbicide exposure.

Hepatobiliary cancers are cancers of the liver and bile duct. There are a variety of risk factors, including hepatitis B and C, alcohol abuse, cirrhosis, exposure to polychlorinated biphenyl (PCB), and smoking, that should be considered by a credible study. NAS, in its 1993 report, found the relevant studies to be few, and to have not adequately controlled for these risk factors. One large case-control study showed a positive relationship between herbicide exposure and the subsequent development of hepatobiliary cancer; however, most other credible studies of similar size indicated no relationship. A large occupational study and a study of farmers found no relationship. See 59 FR 343 for study citations.

NAS noted in its 1996 report that an association between dioxin and liver cancer is biologically plausible, in view of evidence that very high exposures to similar compounds which interact with the Ah receptor (an intracellular protein) increase liver cancer risk. However, NAS concluded in that report that the available evidence is inadequate to determine whether an association exists between exposure to herbicides or dioxin and the incurrence of hepatobiliary cancer. The evidence of biologic plausibility may lend credibility to the evidence for an association between herbicide exposure and liver cancer, but does not itself provide significant evidence of such an association. A case-control study of North Vietnamese veterans (Cordier S., Le T.B., Verger P., Bard D., Le C.D., Larouge B., Dazza M.C., Houng T.Q., Abenhaim L., 1993. Viral infections and chemical exposures as risk factors for hepatocellular carcinoma in Vietnam. International Journal of Cancer 55:196–201) found a significantly increased risk of hepatobiliary cancer (odds ratio (OR) = 8.8, confidence interval (CI) 1.9–41) based on Vietnam service generally. However, investigation of those who had direct contact with aerial sprayings of herbicides yielded a much smaller and nonsignificant OR = 1.3. Also, NAS noted that the value of that study was limited because most cancer cases were diagnosed on clinical or biochemical grounds and were not confirmed histologically. NAS, in its 1996 report, noted that there are few occupational, environmental, or veterans' studies of liver cancer, and most of these are small in size and were not controlled for other risk factors. For example, one small occupational study of workers with potential exposure to TCDD and 4-aminobiphenyl (Collins J.J., Strauss M.E., Levinskas G.J., Connor P.C., 1993. The mortality experience of workers exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin in a trichlorophenal process accident. Epidemiology 4:7–13) showed a slight, but not statistically significant, increased risk for hepatobiliary cancer; however, it did not control for exposure to 4-aminobiphenyl. A large study of herbicide applicators in Finland (Asp S., Riihimaki V., Hernberg S., Pukkala E., 1994. Mortality and cancer morbidity in Finnish chlorophenoxy herbicide applicators: an 18-year prospective follow-up. American Journal of Industrial Medicine 26:243–253) found no increased risk of hepatobiliary cancer. A study of farmers in 23 states (Blair A., Mustafa D., Heineman E.F., 1993. Cancer and other causes of death among male and female farmers from twenty-three states. American Journal of Industrial Medicine 23:729–742) found no increase in proportionate cancer mortality for liver cancer. In summary, most studies that address hepatobiliary cancers suffer from methodological problems or do not reflect an association. 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.

NAS noted in its 1993 report an association between nasal cancers and occupational exposure to nickel and 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 showed inconclusive results, and often did not control for known confounding variables. Pharmacokinetic studies indicate that dioxin accumulates in the nasopharyngeal areas of animals. Two epidemiological studies and one case-control study showed increased risk associated with herbicide exposure; however, two of those studies were statistically insignificant and the small size of the three studies limits their value in detecting an association. (See 59 FR 345 for study citations.) One study (Wiklund K., 1983. Swedish agricultural workers: a group with a decreased risk of cancer. Cancer 51:566–568) found a decreased risk of nasal cancer in Swedish agricultural workers. A study of Vietnam veterans (Centers for Disease Control, 1990. The association of selected cancers with service in the U.S. military in Vietnam. III. Hodgkin's disease, nasal cancer, nasopharyngeal cancer, and primary liver cancer. The Selected Cancers Cooperative Study Group. Archives of Internal Medicine 150:2495–2505) found no association between nasal/nasopharyngeal cancers and Vietnam service. NAS noted in its 1996 report that the scientific evidence concerning an association between herbicide exposure and nasopharyngeal cancer continues to be too sparse to make a definitive conclusion regarding the association of nasal/nasopharyngeal cancers with herbicide exposure. An 18-year follow-up of Finnish herbicide applicators (Asp et al., 1994) showed a small, statistically insignificant increased risk and a decreased mortality risk for cancers of the nasopharynx and larynx. Moreover, that study presented little data and combined cancers of the nasopharynx and larynx into a single category, which diminishes its importance regarding the relationship between herbicide exposure and nasopharyngeal cancers. An environmental study based on a follow-up of the Seveso, Italy, population (Bertazzi A., Pesatori A.C., Consonni D., Tironi A., Landi M.T., Zocchetti C., 1993. Cancer incidence in a population accidentally exposed to 2,3,7,8-tetrachlorodibenzo-para-dioxin. Epidemiology 4:398–406) found a statistically insignificant increased risk for cancer of the nose and nasal cavity among women in the least-contaminated area and found no cases among men in the same area (although 1.5 were expected) and no cases in the most-contaminated areas. Accordingly, the Secretary has found that the credible evidence against an association between nasal/nasopharyngeal 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 in the 1993 NAS report. Because of the rarity of bone cancers, most studies were too small to detect a significant risk. There was not a consistent finding of bone cancer in exposed groups; a number of studies showed no association, and the few studies that demonstrated a positive relationship were small and had large confidence intervals. The small size of the studies and the statistical limitations compromised their credibility. (See 59 FR 343 for study citations.) NAS noted in its 1996 report only two new studies that considered bone cancers. Both studies (Collins et al., 1993 and Blair et al., 1993) found nonsignificant increases in mortality rates due to bone cancers. Methodologic problems did not permit NAS to reach a conclusion regarding the presence or absence of an association between bone cancers and exposure to herbicides. 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 in its 1993 report included those of the breast, ovaries, and uterus (including the cervix and endometrium). The data related to women and herbicide exposure were extremely limited because few of the studies included women. Most of the breast cancer studies showed no association. Two studies, both of which failed to control for reproductive histories and had methodological problems, showed a nonsignificant risk for breast cancer. (See 59 FR 343 for study citations.) Because of the public health significance of breast cancer, NAS, in its 1996 report, considered breast cancer separately from the other reproductive cancers. The data relating exposure to herbicides to breast cancer are sparse. In its 1996 report, NAS reviewed four recently published studies (Bertazzi et al., 1993; Blair et al., 1993; Kogevinas M., Saracci R., Winkelman R., Johnson E.S., Bertazzi P.A., Bueno de Mesquita B.H., Kauppinen T., Littorin M., Lynge E., Neuberger M., 1993. Cancer incidence and mortality in women occupationally exposed to chlorophenoxy herbicides, chlorophenols, and dioxins. Cancer Causes and Control 4:547–553; and Dalager M.S., Kang H.K., Thomas T.L., 1995. Cancer mortality patterns among women who served in the military: The Vietnam experience. Journal of Occupational and Environmental Medicine 37:298–305) that showed no increased risk for breast cancer. NAS noted that it was unclear whether the female members of those cohorts had substantial chemical exposure. Accordingly, 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.

In the 1993 report, NAS identified only one small case-control study which found an association with ovarian cancer, but the confidence intervals were very large. See 59 FR 343 for study citation. The larger occupational and farm worker studies generally showed no increased risk for ovarian or uterine cancers. (See, e.g., Ronco G., Costa G., Lynge E., 1992. Cancer risk among Danish and Italian farmers. British Journal of Industrial Medicine 49:220–225; and 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., Winkelmann R., 1991. Cancer mortality in workers exposed to chlorophenoxy herbicides and chlorophenols. Lancet 338:1027–1032.) The 1993 NAS report identified three studies (Saracci et al., 1991; Ronco et al., 1992; and Wiklund, 1983) showing no increased risk for uterine cancer (including cancers of the cervix and endometrium). One study (Lynge E., 1985. A follow-up study of cancer incidence among workers in manufacture of phenoxy herbicides in Denmark. British Journal of Cancer 52:259–270) showed a slightly increased risk for cervical cancer and no increased risk for endometrial cancer. In its 1996 report, NAS reviewed a follow-up study of the Seveso population (Bertazzi et al., 1993) which found no significant increased risk of ovarian or uterine cancer. A study of 701 women occupationally exposed to chlorophenoxy herbicides, chlorophenols, and dioxins (Kogevinas et al., 1993) found one death from each of the following types of cancer: cervical (standardized mortality rate (SMR)=80), uterine nonspecified (SMR=192), and ovarian (SMR=74). However, no confidence intervals were cited. One study (Lynge E., 1993. Cancer in phenoxy herbicide manufacturing workers in Denmark, 1947–87—an update. Cancer Causes and Control 4:261–272) found a statistically significant increase in cervical cancer

among employees of two Danish phenoxy herbicide manufacturing facilities, based on seven cases (standardized incidence rate (SIR)=3.2, CI 1.3–6.6). A study of farmers in 23 states (Blair et al., 1993) found no increase in the proportionate cancer mortality ratio (PCMR) for cervical cancer in white female farmers, but found a significantly increased PCMR in nonwhite female farmers. The Blair study did not correlate the increased PCMR to herbicide exposure and NAS noted that the increased mortality may reflect risks associated with factors other than herbicide exposure. A study of female Vietnam veterans (Dalager et al., 1995) showed a nonsignificant increased risk of uterine cancer. Although the studies cited in the 1996 NAS report provide some evidence of an association between herbicide exposure and cervical cancer, there continues to be a number of significant studies showing no association between herbicide exposure and either ovarian or uterine cancers (including cervical and endometrial cancers). Considering the entire evidence, the Secretary has found that the credible evidence against an association between herbicide exposure and ovarian and uterine cancers outweighs the credible evidence for such an association, and he has determined that a positive association does not exist.

NAS found in its 1993 report that the leather industry, asbestos, cadmium, petroleum products, analgesics, smoking, and obesity are associated with renal cancers. Studies of renal cancers in relation to herbicide exposure have generally produced inconclusive results because of failure to adequately control for these confounding factors. Only one study of agricultural and forest workers showed a significantly increased risk of death from renal cancers; however, the preponderance of studies, including the two largest, showed either no relationship with renal cancers or increased risk which was not significant. (See 59 FR 343 for study citations.) In its 1996 report, NAS reviewed two new studies (Blair et al., 1993; and Visintainer P.F., Barone M., McGee H., Peterson E.L., 1995. Proportionate mortality study of Vietnam-era veterans of Michigan. Journal of Occupational and Environmental Medicine 37:423–428) that showed increased risk for renal cancer that was not significant. A third cohort study (Bertazzi et al., 1993) demonstrated no increased risk of renal cancer in highly exposed individuals. One case-control study (Mellengaard R., Engholm G., McLaughlin J.K., Olsen J.H., 1994. Occupational risk factors for renal-cell carcinoma in Denmark. Scandinavian Journal of Work, Environment, and Health 20:160–165) showed increased risk for renal cancer; however, the results were considered highly uncertain because of the wide confidence limits. Accordingly, the Secretary has found that the credible evidence against an association between renal cancer and herbicide exposure outweighs the credible evidence for such an association, and he has determined that a positive association does not exist.

NAS, in its 1993 report, identified the major risk factors for testicular cancer as undescended testis and other factors, such as genetic abnormalities, infections, etc., which produce atrophy and dysfunction. Occupational and environmental studies found either no association between herbicide exposure and testicular cancer, or increased risk which was not significant. (See 59 FR 343 for study citations.) In its 1996 report, NAS reviewed three new studies (Blair et al., 1993; Bertazzi et al., 1993; and Bullman T.A., Watanabe K.K., Kang H.K., 1994. Risk of testicular cancer associated with surrogate measures of Agent Orange exposure among Vietnam veterans on the Agent Orange Registry. Annals of Epidemiology 4:11–16) that produced results generally consistent with the 1993 findings, i.e., either no association with testicular cancer, or increased risk which was 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.

NAS, in its 1993 report, found that the potential evidence for an association between herbicide exposure and leukemia came from studies of farmers and residents of Seveso, Italy. When farmers were stratified by suspected herbicide exposure, the incidence of leukemia was generally not elevated, and in some cases elevation appeared to be due to factors other than herbicide exposure. Those studies generally did not adequately control for other significant confounding exposures. 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. (See 59 FR 343–44 for study citations.) In its 1996 report, NAS reviewed seven new studies (Kogevinas et al., 1993; Asp et al., 1994; Blair et al., 1993; Bertazzi et al., 1993; Visintainer et al., 1995; Semenciw R.M., Morrison H.I., Morrison D., Mao Y., 1994. Leukemia mortality and farming in the prairie provinces of Canada. Canadian Journal of Public Health 85:208–211; and Dean G., 1994. Deaths from primary brain cancers, lymphatic and haematopoietic cancers in agricultural workers in the Republic of Ireland. Journal of Epidemiology and Community Health 48:364–368). Six of these studies showed no association between herbicide exposure and leukemia or a nonsignificant elevated risk. Blair et al. (1993), a mortality study of farmers, showed a significantly increased PCMR for leukemia. The Blair study, however, did not correlate the increased PCMR to suspected herbicide exposure and did not control for other confounding factors. 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.

Infertility 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. The 1993 NAS report found no occupational or environmental studies that examined herbicide exposure and infertility, and veteran studies did not support an association between herbicide exposure and infertility. There are several components of male fertility, including sperm parameters and reproductive hormones. The common parameters used to evaluate toxic effects to sperm are number, motility, structure, and morphology. NAS found in its 1993 report that many chemicals have been implicated in interfering with motility and sperm structure. One occupational study and one study of Vietnam veterans found no association with decreased sperm count. Another study of Vietnam veterans found lower sperm concentrations and reduced sperm motility, but suggested these outcomes may be associated with the Vietnam experience rather than exposure to herbicides. NAS did not cite any studies concerning male reproductive hormone levels in its 1993 report. (See 59 FR 344 for study citations.) NAS, in its 1996 report, reviewed one occupational study (Egeland G.M., Sweeney M.H., Fingerhut M.A., Wille K.K., Schnorr T.M., Halperin W.E., 1994. Total serum testosterone and gonadotropins in workers exposed to dioxin. American Journal of Epidemiology 139:272–281 and Egeland G.M., Sweeney M.H.,

Fingerhut M.A., Wille K.K., Schnorr T.M., Halperin W.E., 1995. Reply to letter to the editor. American Journal of Epidemiology 141:477–478); and, although it suggested an association between TCDD exposure and changes in male reproductive hormones, there were a number of methodologic concerns that did not permit definitive conclusions to be drawn. NAS noted that the hormonal changes were subtle, and it is not known whether they would have any implications for reproductive failure. 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.

NAS found in its 1993 report that the studies of cognitive and neuropsychiatric disorders were 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, those studies lacked credibility in assessing the relationship of herbicide exposure to these conditions. The 1996 NAS report reviewed one study (Peper M., Klett M., Frentzel-Beyme R., Heller W.D., 1993. Neuropsychological effects of chronic exposure to environmental dioxins and furans. Environmental Research 60:124–135) that found multiple neuropsychological changes; however, the significance of these findings is uncertain because of the small number of subjects, possible selection bias, the lack of an external control group, and the low estimated amount of exposure. Another reviewed study of a large sample of Vietnam veterans (Decoufle P., Holmgreen P., Boyle C.A., Stroup N.E., 1992. Self-reported health status of Vietnam veterans in relation to perceived exposure to herbicides and combat. American Journal of Epidemiology 135:312–323) found reports of psychological dysfunction correlated with self-reports of combat exposure and level of herbicide exposure. Without confirmation of the subject reports, the significance of these results is in doubt. Because of methodological problems with the preceding studies and two other reviewed studies (Zober A., Ott M.G., Messerer P., 1994. Morbidity follow up study of BASF employees exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) after a 1953 chemical reactor incident. Occupational and Environmental Medicine 51:469–486; and Visintainer et al., 1995), there continues to be no credible evidence for an association between herbicide exposure and cognitive disorders or neuropsychiatric effects. Accordingly, the Secretary has determined that a positive association does not exist.

NAS indicated in its 1993 report that it had found no significant studies available to analyze whether an association exists between herbicide exposure and motor/coordination dysfunction. NAS, in its 1996 report, reported finding no new studies directly addressing this topic. 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.

Chronic peripheral nervous system disorders (chronic peripheral neuropathy) can be induced by many common medical and environmental disorders unrelated to herbicide exposure, such as alcoholism, diabetes, and exposure to other toxic chemicals. NAS, in its 1993 report, stated that many case reports suggested that acute or subacute (transient) peripheral neuropathy can develop with exposure to dioxin, but that the most rigorously conducted studies argued against a relationship between dioxin or herbicides and chronic peripheral neuropathy. NAS's first report stated that, as a group, the studies on peripheral neuropathy suffered from various methodologic defects, such as not applying consistent methods to define a comparison group, determine exposure, evaluate clinical deficits, use standard definitions of peripheral neuropathy, or eliminate confounding variables. Occupational studies that 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. (See 59 FR 343 for study citations.)

NAS, in its 1996 report, assigned acute and subacute peripheral neuropathy to the category labeled limited/suggestive evidence of an association with herbicide exposure, 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. However, NAS continued to assign chronic peripheral neuropathy to the category labeled inadequate/insufficient evidence to determine whether an association exists. Two case studies (Todd R.L., 1962. A case of 2,4–D intoxication. Journal of the Iowa Medical Society 52:663–664; and Berkley M.C., Magee K.R., 1963. Neuropathy following exposure to a dimethylamine salt of 2,4–D. Archives of Internal Medicine 111:133–134) reported development of peripheral neuropathies within days of exposure to 2,4–D followed by gradual recovery over a period of months. Studies of the Seveso, Italy, accident (Boeri R., Bordo B., Crenna P., Filippini G., Massetto M., Zecchini A., 1978. Preliminary results of a neurological investigation of the population exposed to TCDD in the Seveso region. Rivista di Patologia Nervosa e Mentale 9:111–128; 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 Science 320:311–320; and Filippini G., Bordo B., Crenna P., 1981. Relationship between clinical and electrophysiological findings and indicators of heavy exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin. Scandinavian Journal of Work, Environment, and Health 7:257–262) suggested that peripheral nerve problems were more prevalent in the exposed group. Filippini et al. (1981) demonstrated that those individuals with clinical signs of significant exposure (chloracne or elevated liver enzymes) showed a risk ratio of 2.8. Two subsequent follow-up studies (Barbieri S., Pirovano C., Scarbato G., Tarchini P., Zappa A., Maranzana M., 1988. Long-term effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin on the peripheral nervous system. Clinical and neurophysiological controlled study on subjects with chloracne from the Seveso area. Neuroepidemiology 7:29–37; and Assennato G., Cervino D., Emmett E.A., Longo G., Merlo F., 1989. Follow-up of subjects who developed chloracne following TCDD exposure at Seveso. American Journal of Industrial Medicine 16:119–125) showed no increased frequency of peripheral neuropathy several years after the accident among the highly exposed group. Environmental studies and case reports suggest that the development of peripheral neuropathy can follow high levels of exposure to herbicides, and that peripheral neuropathy associated with herbicide exposure will manifest very soon after exposure. The trend to recovery in the individual cases

reported and the negative findings of many long-term follow up studies of peripheral neuropathy (e.g., Zober et al., 1994) suggest that, if a neuropathy develops, it resolves with time. Their findings are consistent with others who found no evidence of increased occurrence of chronic persistent peripheral neuropathy after TCDD exposure. Although the Secretary has found a positive association between herbicide exposure and acute and subacute peripheral neuropathy, considering all of the evidence, he has found that the credible evidence against an association between chronic nervous system disorders and herbicide exposure outweighs the credible evidence for such an association, and he has determined that a positive association does not exist.

Metabolic and digestive disorders include diabetes mellitus, hepatic enzyme abnormality, lipid abnormalities, and ulcers. Although NAS found no biological basis to suspect an association between herbicide exposure and diabetes in its 1993 report, abnormal glucose tolerance tests were reported in three studies. While this suggested such an association, the evidence was inconclusive and its credibility was questionable because an abnormal glucose tolerance test is not an absolute indicator of diabetes and none of the studies allowed for the confounding role of obesity. Two other studies found no association, and a number of studies showed no increased death rates from diabetes. Two 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 did not control for the confounding variables of obesity and genetic factors, and no medical significance of the modest and variable increases was demonstrated. The risk of gastric ulcers in exposed populations was not sufficiently studied to establish an association with herbicide exposure. Only one study indicated any increase, and in that study it was 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. (See 59 FR 344–45 for study citations.) In its 1996 report, NAS reviewed two studies of workers at a BASF plant who had been potentially exposed to TCDD and other chemicals in a plant accident in 1953 (Ott M.G., Zober A., Germann C., 1994. Laboratory results for selected target organs in 138 individuals occupationally exposed to TCDD. Chemosphere 29:2423–2437; and Zober et al., 1994) for any relationship between herbicide exposure and diabetes. Ott et al. (1994) showed a marginal elevation in fasting serum glucose levels, but did not control for obesity. Zober et al. (1994) demonstrated no increase in diabetes with chloracne severity or TCDD levels, and the study did not control for obesity. A third study, involving employees of six chemical factories in Germany (Von Benner A., Edler L., Mayer K., Zober A., 1994. ''Dioxin'' investigation program of the chemical industry professional association. Arbeitsmedizin Sozialmedizin Praventivmedizin 29:11–16) showed no correlation between serum TCDD levels and blood glucose levels. In its 1996 report, NAS reviewed the same three studies (Ott et al., 1994; Zober et al., 1994; and Von Benner et al., 1994) when considering the relationship between herbicide exposure and hepatic enzyme abnormalities. The noted increases in abnormal liver function tests or the frequency of chronic liver disease were confounded by the lack of control for alcohol abuse. Zober, et al. (1994) found a nonsignificant increase in liver disease among individuals exposed to dioxin, and Von Benner, et al. (1994) found no correlation between serum dioxin levels and abnormalities in liver function tests. One new study was reviewed in the 1996 NAS report concerning any association between herbicide exposure and lipid abnormalities (Ott et al., 1994) and showed no substantial differences between the exposed and reference groups. The only new study reviewed in the 1996 NAS report concerning any relationship between ulcers and exposure to herbicides (Zober et al., 1994) showed no increases in the frequency of ulcers. Accordingly, the Secretary has found that the credible evidence against an association between metabolic and digestive disorders and herbicide exposure outweighs the credible evidence for such an association, and he has determined that a positive association does not exist.

NAS found, in its 1993 report, that the available data dealt with two categories of immune system disorders: immune modulation and autoimmunity. Many immune parameters were studied; however, few showed a relationship to herbicide exposure. Most studies addressed such a wide range of immune parameters that it was likely that at least some of the positive results were due to chance alone. Other studies found no relationship between immune system disorders and herbicide exposure. (See 59 FR 345 for study citations.) NAS noted in its 1996 report that no new studies of heightened susceptibility to infectious disease or new studies that investigated the association of autoimmune disease with exposure to herbicides have been identified. However, some new information has been published regarding the effects of TCDD on immunological parameters in laboratory measurements. The new studies (Ott et al., 1994; Von Benner et al., 1994; Jansing P.J., Korff R., 1994. Blood levels of 2,3,7,8-tetrachlorodibenzo-p-dioxin and gamma-globulins in a follow-up investigation of employees with chloracne. Journal of Dermatological Science 8:91–95; Svenson B.G., Hallberg T., Nilsson A., Schutz A., Hagmar L., 1994. Parameters of immunological competence in subjects with high consumption of fish contaminated with persistent organochlorine compounds. International Archives of Occupational and Environmental Health 65:351–358; Neubert R., Maskow L., Webb J., Jacob-Muller U., Nogueira A.C., Delgado I., Helge H., Neubert D., 1993. Chlorinated dibenzo-p-dioxins and dibenzofurans and the human immune system. 1. Blood cell receptors in volunteers with moderately increased body burdens. Life Sciences 53:1995–2006; and Neubert R., Maskow L., Delgado I., Helge H., Neubert D., 1994. Chlorinated dibenzo-p-dioxins and dibenzofurans and the human immune system. 2. In vitro proliferation of lymphocytes from workers with quantified moderately increased body burdens. Life Sciences 56:421–436) reviewed such a wide range of immune parameters that it is likely that at least some of the abnormal laboratory tests were due to chance. In addition, these studies failed to show a relationship between laboratory abnormalities and development of disease in the populations studied. 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.

NAS noted in its 1993 report that most occupational studies concerning circulatory disorders showed no increased mortality or morbidity after herbicide exposure. The studies of the residents of Seveso, Italy, showed some increased risk of mortality in the first five-year follow-up; however, those 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. Certain of the veteran studies suggested that any increase in heart disease may be associated with the Vietnam experience rather than herbicide exposure, and most of those studies did not adjust for confounding variables. (See 59 FR 345 for study citations.) NAS reviewed one study (Zober et al., 1994) in its 1996 report that showed no increase in the frequency of heart disease. Another study (Von Benner, et al., 1994) found possible correlations for elevated systolic blood pressure; however, this relationship was difficult to evaluate because age and body-mass index also had a significant effect. An analysis (Wolfe W.H., Michalek J.E., Miner J.C., Roegner R. H., Grubbs W.D., Lustik M.B., Brockman A.S., Henderson S.C., Williams D.E., 1992. The air force health study: An epidemiologic investigation of health effects in Air Force personnel following exposure to herbicides, serum dioxin analysis of 1987 examination results. Chemosphere 25:213–216) of the data from an Air Force study (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. 9 vols. Brooks AFB, TX: USAF School of Aerospace Medicine) provides some potentially significant evidence for an association with dioxin exposure, since the results were derived from the first large-scale study of dose-response relationships. However, this study did not control for the confounding factor of diabetes. There was a significant increased risk of essential hypertension for the participants with a high-level of dioxin exposure. However, the reverse analysis of participants suffering from hypertension did not show an association with dioxin, suggesting lack of dose-response relationships. Accordingly, the Secretary has found that the credible evidence against an association between circulatory disorders and herbicide exposure outweighs the credible evidence for such an association, and he has determined that a positive association does not exist.

In its 1993 report, NAS examined studies that covered a wide variety of respiratory disorders (e.g., chronic bronchitis, asthma, pleurisy, pneumonia, and tuberculosis), other than respiratory cancers. Studies of individuals exposed in occupational settings revealed no increase in mortality from respiratory disease. Environmental exposure studies similarly showed no significant differences in mortality due to respiratory disease. Mortality studies of Vietnam veterans generally found no increased risk. Morbidity data were generally difficult to evaluate because of methodological problems and because studies focused on symptoms, lung function tests and x-ray interpretation rather than disease. One occupational study showed no excess morbidity; another occupational study found increased symptomatology of respiratory disease, but did not adequately control for the confounding factor of age. (See 59 FR 345 for study citations.) NAS, in its 1996 report, reviewed three new studies (Zober et al., 1994; Garry V.F., Kelly J.T., Sprafka J.M., Edwards S., Griffith J., 1994. Survey of health and use characterization of pesticide appliers in Minnesota. Archives of Environmental Health 49:337–343; and Senthilselvan A., McDuffie H.H., Dosman J.A., 1992. Association of asthma with use of pesticides: results of a cross-sectional survey of farmers. American Review of Respiratory Diseases 146:884–887), all of which found no significant increase in respiratory disease associated with herbicide exposure. Accordingly, the Secretary has found that the credible evidence against an association between respiratory disorders (other than certain respiratory cancers) and herbicide exposure outweighs the credible evidence for such an association, and he has determined that a positive association does not exist.

NAS, in its 1993 report, assigned skin cancer to a category labeled limited/suggestive evidence of no association with herbicide exposure. This is 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. There were many credible studies that showed no association or a negative association with herbicide exposure. (See Chapter 8 of NAS's first report.) The 1996 NAS report reviewed one new study (Lynge, 1993) that did find an excess risk of skin cancer. However, another new study (Bertazzi et al., 1993) found no increased risk of skin cancer. Three other new studies (Asp et al., 1994; Collins et al., 1993; and Bueno de Mesquita H.B., Doornbos G., Van der Kuip D.A., Kogevinas M., Winkelmann R., 1993. Occupational exposure to phenoxy herbicides and chlorophenols and cancer mortality in the Netherlands. American Journal of Industrial Medicine 23:289–300) were too small to have sufficient statistical power to give definitive results. A mortality study of farmers in 23 states utilizing occupational information from death certificates (Blair et al., 1993) found an increased PCMR for skin cancer in white male farmers. The Blair study, however, did not correlate the increased PCMR to suspected herbicide exposure and did not control for other confounding factors. NAS felt that these studies, while not providing suggestive evidence of an association with herbicide exposure, undermined the evidence of no association discussed in its first report, and thus warranted changing skin cancer from the ''limited/suggestive evidence of no association'' category to the ''inadequate/insufficient evidence to determine whether an association exists'' category. Based on the available evidence, the Secretary has found that the credible evidence against an association between skin cancer and herbicide exposure outweighs the credible evidence for such an association, and he has determined that a positive association does not exist.

NAS, in its 1996 report (as it had in its 1993 report), also reviewed the current literature with respect to possible associations between herbicide exposure and various reproductive effects, i.e., spontaneous abortion, spina bifida, birth defects (other than spina bifida), neonatal/infant deaths and stillbirths, low birthweights, and childhood cancer in offspring. Compensation of a veteran or a veteran's child for these effects is beyond VA's authority (See title 38, U.S.C.) and would require enabling legislation.

NAS, in its 1996 report, assigns three diseases or categories of diseases to a category labeled limited/suggestive evidence of no association with herbicide exposure, which it defined in the same manner as in the 1993 NAS report (see above). The conditions include gastrointestinal tumors (stomach cancer, pancreatic cancer, colon cancer, and rectal cancer), bladder cancer, and brain tumors. There were many credible studies (see the 1996 NAS report, Chapter 7) concerning all of these conditions that showed no association or a negative association with herbicide exposure. Accordingly, the Secretary has found that the credible evidence against an association between gastrointestinal tumors (stomach cancer, pancreatic cancer, colon cancer, and rectal cancer), bladder cancer, and brain tumors and herbicide exposure outweighs the credible evidence for such an association, and he has

determined that a positive association does not exist.

NAS reviewed scientific and medical articles published since the publication of its first report as an integral part of the process that resulted in ''Veterans and Agent Orange: Update 1996.'' In our judgment, the comprehensive review and evaluation of the available literature which NAS conducted in conjunction with its report has permitted VA 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.

Approved: July 8, 1996.

Jesse Brown,

Secretary of Veterans Affairs.

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