

## II. Matters That May Be Addressed in Additional Comments

The revised Ordinance amends, relocates and removes several provisions that AWHMT challenges in its application. The revised Ordinance also creates a new Article XVII, which is entitled "Waste Transporters".

In accordance with 49 CFR 107.219(a), RSPA invites all interested parties to comment on the revised Ordinance.

It appears that the revised Ordinance substantially modifies the previous version of the Ordinance. Therefore, in accordance with 49 CFR 107.219(b), AWHMT is directed to supplement its application, to the extent necessary, to reflect the recent revisions to the Ordinance. For example, AWHMT should ensure that the revisions to the Ordinance have not affected its substantive arguments and it should ensure the accuracy of its citations to particular provisions of the Ordinance.

Issued in Washington, D.C. on October 27, 1999.

**Alan I. Roberts,**

*Associate Administrator for Hazardous Materials Safety.*

[FR Doc. 99-28615 Filed 11-1-99; 8:45 am]

BILLING CODE 4910-60-P

## DEPARTMENT OF THE TREASURY

### Office of the Comptroller of the Currency

#### Proposed Renewal of Information Collection; Comment Request

**AGENCY:** Office of the Comptroller of the Currency (OCC), Treasury.

**ACTION:** Notice and request for comments.

**SUMMARY:** The OCC, as part of its continuing effort to reduce paperwork and respondent burden, invites the general public and other Federal agencies to take this opportunity to comment on a continuing information collection, as required by the Paperwork Reduction Act of 1995. Currently, the OCC is soliciting comments concerning its extension, without change, for an information collection titled, "(MA)—Securities Exchange Act Disclosure Rules—12 CFR 11."

**DATES:** You should submit written comments by January 2, 2000.

**ADDRESSES:** You should direct all written comments to the Communications Division, Attention: 1557-0106, Third Floor, Office of the Comptroller of the Currency, 250 E Street, SW, Washington, DC 20219. In

addition, you may send comments by facsimile transmission to (202) 874-5274, or by electronic mail to [regs.comments@occ.treas.gov](mailto:regs.comments@occ.treas.gov).

**FOR FURTHER INFORMATION CONTACT:** You can request additional information or a copy of the collection from Jessie Dunaway or Camille Dixon, (202) 874-5090, Legislative and Regulatory Activities Division (1557-0106), Office of the Comptroller of the Currency, 250 E Street, SW, Washington, DC 20219.

**SUPPLEMENTARY INFORMATION:** The OCC is proposing to extend OMB approval of the following information collection:

*Title:* (MA)—Securities Exchange Act Disclosure Rules—12 CFR 11.

*OMB Number:* 1557-0106.

*Form Number:* SEC Forms 3, 4, 5, 8-K, 10, 10-K, 10-Q, Schedules 13D, 13G, 14A, 14B, and 14C.

*Abstract:* This information collection covers the OCC's Securities Exchange Act Disclosure Rules (12 CFR part 11) which require national banks to make public disclosures and file with the OCC certain Securities Exchange Commission forms. Publicly-owned national banks must make disclosures and filings to comply with applicable banking and securities law and regulatory requirements. The OCC reviews the information to ensure that it complies with Federal law and makes public all information required to be filed. Investors, depositors, and the public use the information to make informed investment decisions.

*Type of Review:* Extension, without change, of a currently approved information collection.

*Affected Public:* Businesses or other for-profit.

*Estimated Number of Respondents:* 131.

*Estimated Total Annual Responses:* 636.

*Frequency of Response:* Occasional.

*Estimated Total Annual Burden*

*Hours:* 5,360.

#### Comments

Comments submitted in response to this notice will be summarized and included in the request for OMB approval. All comments will become a matter of public record. Comments are invited on:

(a) Whether the collection of information is necessary for the proper performance of the functions of the agency, including whether the information has practical utility;

(b) The accuracy of the OCC's estimate of the burden of the collection of information;

(c) Ways to enhance the quality, utility, and clarity of the information to be collected;

(d) Ways to minimize the burden of the collection on respondents, including through the use of automated collection techniques or other forms of information technology; and

(e) Estimates of capital or startup costs and costs of operation, maintenance, and purchase of services to provide information.

Dated: October 27, 1999.

**Mark Tenhundfeld,**

*Assistant Director, Legislative & Regulatory Activities Division.*

[FR Doc. 99-28571 Filed 11-1-99; 8:45 am]

BILLING CODE 4810-33-P

## DEPARTMENT OF VETERANS AFFAIRS

### Diseases 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, breast cancer, female reproductive cancers, urinary bladder cancer, renal cancer, testicular cancer, leukemia, abnormal sperm parameters and infertility, motor/coordination dysfunction, chronic peripheral nervous system disorders, metabolic and digestive disorders (other than diabetes mellitus), immune system disorders, circulatory disorders, respiratory disorders (other than certain respiratory cancers), skin cancer, cognitive and neuropsychiatric effects, gastrointestinal tumors, 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:** Donald England, Chief, Regulations Staff, Compensation and Pension Service, Veterans Benefits Administration, 810 Vermont Avenue, NW., Washington, DC 20420, telephone (202) 273-7210.

**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, bias, and other pertinent characteristics, some studies are clearly more credible than others, and the Secretary has given the more credible studies more weight in evaluating the overall weight of the evidence concerning specific diseases.

NAS issued its initial report, entitled "Veterans and Agent Orange: Health Effects of Herbicides Used in Vietnam," (VAO) on July 27, 1993. The Secretary subsequently determined that a positive association exists between exposure to herbicides used in the Republic of Vietnam and the subsequent development of Hodgkin's disease, porphyria cutanea tarda, multiple myeloma, and certain respiratory cancers; and that there was no positive association between herbicide exposure and any other condition, other than chloracne, non-Hodgkin's lymphoma, and soft-tissue sarcomas, for which presumptions already existed. A notice of the diseases that the Secretary determined were not associated with exposure to herbicide agents was published on January 4, 1994 (See 59 FR 341-46).

NAS issued its second report, entitled "Veterans and Agent Orange: Update 1996" (Update 1996), on March 14, 1996. The Secretary subsequently determined that a positive association exists between exposure to herbicides used in the Republic of Vietnam and the subsequent development of prostate cancer and acute and subacute peripheral neuropathy in exposed persons. The Secretary further determined that there was no positive association between herbicide exposure and any other condition, other than those for which presumptions already existed. A notice of the diseases that the Secretary determined were not associated with exposure to herbicide agents was published on August 8, 1996 (See 61 FR 41442-49).

NAS issued a third report, entitled "Veterans and Agent Orange: Update 1998" (Update 1998), on February 11, 1999. The focus of this updated review was on new scientific studies published since the release of Update 1996 and updates of scientific studies previously reviewed.

Shortly after NAS issued Update 1998, the Secretary formed a VA task force to review the report and pertinent studies and to make recommendations to assist him in determining whether a positive association exists between

herbicide exposure and any condition. The task force has completed that review and submitted its recommendations 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, breast cancer, female reproductive cancers, urinary bladder cancer, renal cancer, testicular cancer, leukemia, abnormal sperm parameters and infertility, motor/coordination dysfunction, chronic peripheral nervous system disorders, metabolic and digestive disorders (other than diabetes mellitus), immune system disorders, circulatory disorders, respiratory disorders (other than certain respiratory cancers), skin cancer, cognitive and neuropsychiatric effects, gastrointestinal tumors, brain tumors, and any other condition for which the Secretary has not specifically determined a presumption of service connection is warranted.

This notice also conveys the Secretary's determination that a new study concerning the possible association between exposure to herbicides and diabetes mellitus that was published since NAS completed Update 1998, is potentially significant. The Secretary has requested, and the NAS is currently reviewing that new study and will determine whether a positive association exists between herbicide exposure and diabetes mellitus after their review.

NAS, in Update 1998, assigns hepatobiliary cancers, nasal/nasopharyngeal cancer, bone cancer, breast cancer, female reproductive cancers, urinary bladder cancer, renal cancer, testicular cancer, leukemia, abnormal sperm parameters and infertility, motor/coordination dysfunction, chronic peripheral nervous system disorders, metabolic and digestive disorders (including diabetes mellitus), 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 power to permit a conclusion regarding the presence or absence of an association with herbicide exposure.

#### **Hepatobiliary Cancers**

Hepatobiliary cancers are cancers of the liver and intrahepatic bile ducts. There are a variety of known risk

factors, including chronic infections with hepatitis B and C, exposure to aflatoxin, vinyl chloride and polychlorinated biphenyl (PCB) and smoking, that should be considered by a credible study. NAS, in VAO, 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 Update 1996 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. NAS, in Update 1996, again 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 et al., 1993) 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 et al., 1994) found no increased risk of hepatobiliary cancer. A study of farmers in 23 states (Blair et al., 1993) found no increase in proportionate cancer mortality for liver cancer. In summary, most studies that addressed hepatobiliary cancers suffered from methodological problems or did not reflect an association. See 61 FR 41443 for study citations.

NAS, in Update 1998, again assigned hepatobiliary cancer to the category "inadequate/insufficient evidence to determine whether an association exists." The IARC study (Kogevinas M, Becher H, Benn T, Bertazzi PA, Boffetta P, Bueno-de-Mesquita HB, Coggon D, Colin D, Flesch-Janys D, Fingerhut M, Green L, Kauppinen T, Lettorin M,

Lynge E, Mathews JD, Neuberger M, Pearce N, Saracci R. 1997. Cancer mortality in workers exposed to phenoxy herbicides, chlorophenols, and dioxins. An expanded and updated international cohort study. *American Journal of Epidemiology* 145(12): 1061–1075.) noted no excess of death from hepatobiliary cancer among a group of all workers exposed to phenoxy herbicides or chlorophenol, although those exposed to TCDD or higher chlorinated dioxins had a higher risk (SMR=0.87, CI 0.45–1.52) than those not exposed (SMR=0.41, CI 0.09–1.22). However, this study did not include a detailed analysis by exposure variables (such as duration and time since first exposure), and did not distinguish heavily exposed workers from those with minor exposures. A study of 2,479 male workers in German facilities that produced phenoxy herbicides and chlorophenols (Becher H, Flesch-Janys D, Kauppinen T, Kogevinas M, Steindorf K, Manz A, Wahrendorf J. 1996. Cancer mortality in German male workers exposed to phenoxy herbicides and dioxins. *Cancer Causes and Control* 7(3): 312–21.) showed only one death due to hepatobiliary cancer (SMR=1.2, CI 0–6.9); this was in one of the groups with presumed lower TCDD exposure. Observed and expected deaths due to liver cancer among a cohort of rice growers in northern Italy between 1957 and 1992 (Gambini GF, Mantovani C, Pira E, Piolatto PG, Negri E. 1997. Cancer mortality among rice growers in Novara Province, Northern Italy. *American Journal of Industrial Medicine* 31(4): 435–441.) did not differ significantly from national rates (SMR=1.3, CI 0.5–2.6). This small study is limited by its crude exposure assessment and uncertainty in establishing degree of exposure. A 15-year follow-up of the exposed population of Seveso, Italy (Bertazzi PA, Zocchetti C, Guercilena S, Consonni D, Tironi A, Landi MT, Pesatori AC. 1997. Dioxin exposure and cancer risk: A 15-year mortality study after the "Seveso Accident." *Epidemiology* 8(6): 646–652) showed nonsignificant decreases in liver cancer in all exposure groups except for women in group B, where a nonsignificant elevation was seen (3 cases for an SMR=1.3, CI 0.3–3.8). A study of two cohorts of Swedish fishermen, distinguished by the types of fish in their diets and the presumed levels of PCB, PCDD, and PCDF in the fish (Svennson BG, Mikoczy Z, Stromberg U, Hagmar L. 1995. Mortality and cancer incidence among Swedish fishermen with a high dietary intake of persistent organochlorine compounds.

*Scandinavian Journal of Work, Environment, and Health* 21(2): 106–115.), showed nonsignificantly decreased mortality from liver cancer in both groups. The group presumed to have higher exposure had a nonsignificantly increased incidence of the disease compared to national Swedish rates (SIR=1.31, CI 0.48–2.85), while the less exposed group had a nonsignificantly decreased incidence. A particular weakness of this study is the lack of data to support the differences in reported blood levels of dioxin-like compounds for each group. A study of male Australian Vietnam veterans (Crane PJ, Horsley KD, Adena MA. 1997a. Mortality of Vietnam veterans: the veteran cohort study: A report of the 1996 retrospective cohort study of Australian Vietnam veterans, Canberra; Department of Veterans Affairs.) reported a statistically significant excess of all cancer deaths among the 2,067 deaths recorded from 1980 to 1994 but observed no excess of mortality from liver cancer (SMR=0.6, CI 0.3–1.2). However, among the weaknesses of this study are the possible under ascertainment of death, and the uncertain quality of assessing such risk factors as smoking, alcohol, and herbicide and dioxin exposure. Crane's subsequent study of mortality among Australian National Service Vietnam veterans reported similar findings for hepatobiliary cancer (Crane PJ, Horsley KD, Adena MA. 1997b. Mortality of Vietnam veterans: the national servicemen comparison. A report of the 1996 retrospective cohort study of Australian Vietnam veterans. Canberra; Department of Veterans Affairs.)

Most of the few existing studies addressing hepatobiliary cancer contain methodological difficulties such as small study size and inadequate control for life-style-related risk factors, or do not support an association with herbicide exposure. 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.

#### Nasal/Nasopharyngeal Cancer

NAS noted that exposure to nickel, chromates, wood dust and formaldehyde are risk factors for nasal cancers. Smoking, exposure to salt-preserved foods, and Epstein-Barr virus may increase the risk of nasopharyngeal cancer.

In VAO, NAS found studies of nasal and nasopharyngeal cancers very limited. 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. One study (Wiklund K., 1983) found a decreased risk of nasal cancer in Swedish agricultural workers. A study of Vietnam veterans (Centers for Disease Control, 1990) found no association between nasal/nasopharyngeal cancers and Vietnam service. (See 59 FR 345 for study citations.)

NAS noted in Update 1996 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 et al., 1993) 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. (See 61 FR 41443-44 for study citations.)

In Update 1998, NAS stated that scientific evidence of an association with herbicide exposure continues to be too sparse to make a definitive statement. The IARC study (Kogevinas et al., 1997) has brought together almost all of the phenoxy herbicide production workers in 36 cohorts for a joint analysis. That combined cohort study showed no effect of phenoxy herbicide exposure on oral cavity or pharyngeal cancers (RR=1.1, CI 0.7-1.6). There were three deaths from cancer of the nose and nasal sinuses, but none in the TCDD-exposed group (RR=1.6, CI 0.3-4.7). Crane et al. (1997a) found no deaths from either nasal or nasopharyngeal cancer in Australian Vietnam veterans during 1964-1979, with 0.8 expected.

For the period 1980-1994, there were two deaths due to nasal and two due to nasopharyngeal cancers, with 1.7 and 3.9 expected, respectively. Crane's companion study comparing Australian Vietnam veterans with military personnel who did not serve there showed one death due to nasopharyngeal cancer in each group between 1982-1994, and only one death due to nasal cancer, which occurred in the comparison population (Crane et al., 1997b). NAS found that the scientific evidence of the association between herbicide exposure and nasopharyngeal cancer continues to be too sparse to make a definitive statement.

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**

Bone cancers were considered together with joint cancers in VAO. 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 Update 1996 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. (See 61 FR 41444 for study citations.)

In Update 1998, NAS reports that there is minimal new information regarding bone cancer and that few data existed before. A study of the IARC combined occupational cohorts (Kogevinas et al., 1997) found five cases of bone cancer for all workers (SMR=1.2, CI 0.4-2.8). The SMR in those exposed to TCDD was lower (1.1) than in those not exposed (1.4). A study of 770 pentachlorophenol workers reported no deaths from bone cancer (Ramlow JM, Spadacene JW, Hoag SR, Stafford BA, Cartmill JB, Lerner PJ. 1996. Mortality in a cohort of pentachlorophenol manufacturing workers, 1940-1989. American Journal

of Industrial Medicine 30(2): 180-194.). A study of rice growers in northern Italy (Gambini et al., 1997) identified only one death, and a study of 26,000 Canadian sawmill workers presumptively exposed to dioxin-contaminated chlorophenate reported five bone cancer deaths (SMR=1.3, CI 0.5-2.7) (Hertzmann C, Teschke K, Ostry A, Hershler R, Dimich-Ward H, Kelly S, Spinelli JJ, Gallagher RP, McBride M, Marion SA. 1997. Mortality and cancer incidence among sawmill workers exposed to chlorophenate wood preservatives. American Journal of Public Health 87(1): 71-79.). A follow-up of individuals exposed as a result of the 1976 industrial accident in Seveso, Italy, found 2 deaths in men (SMR=0.5) in the lowest exposure zone and 7 deaths in women in the lowest exposure zone (SMR=2.4) (Bertazzi et al., 1997). Clapp's update of his study of Massachusetts Vietnam veterans reports 4 cases of bone cancer (OR=0.9, CI 0.1-11.3) (Clapp RW. 1997. Update of cancer surveillance of veterans in Massachusetts, USA. International Journal of Epidemiology 26(3): 679-681.). Other Vietnam veteran studies did not report bone cancer results. After reviewing all available evidence, 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.

#### **Breast Cancer and Female Reproductive Cancers**

The data related to women and herbicide exposure have been extremely limited because few of the studies have included women. Cohorts reviewed in occupational studies have included few exposed female workers.

Female reproductive cancers reviewed by NAS in VAO included those of the breast, ovaries, and uterus (including the cervix and endometrium). Because of the public health significance of breast cancer, NAS, in Update 1996, considered breast cancer separately from the other reproductive cancers. In Update 1998, NAS again addresses breast cancer separately from the other cancers.

#### *Breast Cancer*

Risk factors for breast cancer include age, race, personal or family history of breast cancer and reproductive history. The data relating exposure to herbicides to breast cancer are sparse. In VAO, NAS found that 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.)

In Update 1996, NAS reviewed four recently published studies (Bertazzi *et al.*, 1993; Blair *et al.*, 1993; Kogevinas *et al.*, 1993, and Dalager *et al.*, 1995) 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. (See 61 FR 41444 for study citations.)

NAS found few new published studies on breast cancer since Update 1996. The IARC study (Kogevinas *et al.*, 1997) found a nonsignificant increased risk of breast cancer in males, as well as a significant increased risk in one cohort of women from Germany with substantial exposure to TCDD or higher chlorinated dioxins. Data from Australian Vietnam veterans (Crane *et al.*, 1997a) also indicated an elevation of male breast cancer (SMR=5.5, 95% CI 1.1–16.1). The findings of increased risk for males are notable because breast cancer in males is rare. On the other hand, the 15-year follow-up of the Seveso population (Bertazzi *et al.*, 1997) indicates no excess of breast cancer, and even suggests a possible protective effect of TCDD exposure (RR less than 1.0). TCDD also appears to exert a protective effect on the incidence of mammary tumors in experimental animals. Taken together, the data continue to be inconclusive. 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.

#### *Female Reproductive Cancers (Ovaries, Uterus, Cervix, Endometrium)*

In VAO, NAS identified only one small case-control study which found an association with ovarian cancer, but the confidence intervals were very large. The larger occupational and farm worker studies generally showed no increased risk for ovarian or uterine cancers. VAO identified three studies showing no increased risk for uterine cancer (including cancers of the cervix and endometrium). One study showed a slightly increased risk for cervical cancer and no increased risk for endometrial cancer. (See 59 FR 343 for study citations.)

In Update 1996, NAS reviewed a follow-up study of the Seveso population which found no significant increased risk of ovarian or uterine cancer. A study of 701 women

occupationally exposed to chlorophenoxy herbicides, chlorophenols and dioxins found one death from each of the following types of cancer: cervical (SMR=80), uterine nonspecified (SMR=192), and ovarian (SMR=74). One study found a statistically significant increase in cervical cancer among employees of two Danish phenoxy herbicide manufacturing facilities, based on seven cases (SIR=3.2, CI 1.3–6.6). A study of farmers in 23 states 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. This 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 showed a nonsignificant increased risk of uterine cancer. Although the studies cited in Update 1996 provided some evidence of an association between herbicide exposure and cervical cancer, there continued to be a number of significant studies showing no association between herbicide exposure and either ovarian or uterine cancers (including cervical and endometrial cancers). (See 61 FR 4144–45 for study citations.)

In Update 1998, NAS reviewed two new studies. A 15-year follow-up of more than 20,000 exposed women in the Seveso population (Bertazzi *et al.*, 1997) provides no evidence that TCDD is associated with deaths from either uterine or ovarian cancer. Deaths from uterine cancer were lower than expected in the two zones with the highest exposures, and the deaths from ovarian cancer were 1 and 0, respectively, where 0.4 and 2.7, respectively, were expected. In one zone with a lower exposure (but still greater than those not exposed to the accident), 27 uterine cancer deaths were observed, where 23.7 were expected (RR=1.1, 95% CI 0.8–1.7). The RR for ovarian cancer in this zone was 1.0 (CI 0.6–1.6). However, it may still be too early for tumors related to exposure to have come to clinical attention. In the IARC study (Kogevinas *et al.*, 1997), no deaths from cancer of the uterine cervix or the ovary were observed among women exposed to TCDD or higher chlorinated dioxins. An SMR of 3.41 was observed for cancer of the endometrium and uterus based on three cases with exposure to TCDD or higher chlorinated dioxins. Two of these cases occurred in the cohort that included most of the TCDD-exposed female production workers. NAS concluded

that despite some strong associations with ovarian and uterine cancers, the evidence remains inconclusive, largely because most of the published studies have only a small number of cases, poor exposure characterization, or too short a follow-up period. 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.

#### **Urinary Bladder Cancer**

Smoking is the most important risk factor for cancer of the urinary bladder. However, exposure to aromatic amines, high fat diet and schistosoma hematobium infection have also been implicated. In VAO and Update 1996, NAS assigned urinary bladder cancer to a category labeled limited/suggestive evidence of no association with herbicide exposure. This category 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. One study found a small excess of mortality in chemical production workers exposed to TCDD. There were many other credible studies that produced inconclusive results. (For study citations, see pages 515–17 of the 1993 report and pages 225–27 of the 1996 report.)

In Update 1998, NAS, on the basis of all epidemiologic evidence, felt that urinary bladder cancer should now be assigned to the category "inadequate/insufficient evidence to determine whether an association exists." The risk ratios (RR) in some of the largest cohorts tended to be greater than 1, weakening the prior conclusion that there was positive evidence of no relationship. The IARC study found an SMR of 1.0 (CI 0.7–1.5) for all workers, and an SMR of 1.4 (CI 0.9–2.1) among workers exposed to TCDD or higher chlorinated dioxins (Kogevinas *et al.*, 1997). A follow-up of BASF employees (Ott MG, Zober A. 1996. Cause specific mortality and cancer incidence among employees exposed to 2,3,7,8-TCDD after a 1953 reactor accident. *Occupational and Environmental Medicine* 53(9): 606–612.) found two deaths from a total of five cases (SIR=1.4, CI 0.4–3.2), but they were described as due to "bladder or kidney" cancer. A cohort of Swedish fisherman with presumed elevated-exposure (Svensson *et al.*, 1995) showed

an SIR of 0.7 (CI 0.4–1.3), while a comparison cohort showed an SIR of 0.9 (CI 0.7–1.1). SMRs for the two cohorts were 1.3 (CI 0.4–3.1) and 1.0 (CI 0.6–1.6), respectively. Other new occupational and environmental studies showed results around the null (Hertzman *et al.*, 1997; Gambini *et al.*, 1997; and Bertazzi *et al.*, 1997). Among Vietnam veteran studies, a study of the mortality experience of Australian veterans relative to military personnel who did not serve in Vietnam reported a statistically significant RR of 0.6 based on one death among Vietnam veterans and two in the comparison group (Crane *et al.*, 1997b). An update of a study of Massachusetts veterans (Clapp, 1997) found an OR of 0.6 (CI 0.2–1.3) based on 80 cases.

On the basis of its review of new studies, NAS found that there is no evidence that exposure to herbicides alone is related to bladder cancer. Exposure to TCDD in combination with other known bladder carcinogens made it difficult to isolate any additional effect of herbicides. Considering the entire evidence, the Secretary has found that the credible evidence against an association between herbicide exposure and urinary bladder cancer outweighs the credible evidence for such an association, and he has determined that a positive association does not exist.

#### Renal Cancer

NAS found in VAO 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 they failed 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 Update 1996, NAS reviewed two new studies (Blair *et al.*, 1993; and Visintainer *et al.*, 1995) 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 Danish case-control study (Mellengaard *et al.*, 1994) showed increased risk for renal cancer; however, the results were considered highly uncertain because of the wide confidence limits. (See 61 FR 41445 for study citations.)

In Update 1998, NAS found that the most important new study was that of the IARC cohorts (Kogevinas *et al.*, 1997). This study reported 26 cases of kidney cancer (SMR=1.6; CI 1.1–2.4) for workers exposed to TCDD, and an SMR of 1.1 (CI 0.7–1.6) for all workers exposed to any phenoxy herbicide or chlorophenol. However, the study provided no trend analysis by duration of exposure or time since exposure. Clapp's update on Massachusetts Vietnam veterans (Clapp, 1997) reported an OR of 1.0 (CI 0.4–2.3). A study comparing all Australian Vietnam veterans to the male Australian population reported SMR=1.2 (CI 0.8–1.9) (Crane *et al.*, 1997a). Another study of Australian Vietnam veterans compared with military personnel who did not serve in the conflict reported a statistically significant RR of 3.9 based on three deaths among Vietnam veterans and one in the comparison population between 1982 and 1984 (Crane *et al.*, 1997b). However, this study did not have exposure information. Other studies reviewed by NAS produced equivocal results. NAS concluded that of the literature published since Update 1996, only the IARC study points to a possible association between herbicide exposure and renal cancer, but that, due to its marginal significance, lack of trend data, and heterogeneity of the cohorts, it was not strong enough to outweigh the equivocal results of the other studies. Therefore, on the basis of all available evidence, 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.

#### Testicular Cancer

In VAO, NAS 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 Update 1996, NAS reviewed three new studies that produced results generally consistent with the 1993 findings, i.e., either no association with testicular cancer, or increased risk which was not significant. (See FR 61 41445 for study citations.)

In Update 1998, NAS found minimal new information on this rare cancer based on a review of 10 new studies (Kogevinas *et al.*, 1997; Ramlow *et al.*,

1996; Hertzman *et al.*, 1997; Bertazzi *et al.*, 1997; Zhong Y, Raffnsson V. 1996. Cancer incidence among Icelandic pesticide users. *International Journal of Epidemiology* 25(6): 1117–1124; Dalager NA, Kang HK. 1997. Mortality among Army Chemical Corps Vietnam veterans. *American Journal of Industrial Medicine* 31(6): 719–726; Watanabe KK, Kang HK. 1996. Mortality patterns among Vietnam veterans: a 24-year retrospective analysis. *Journal of Occupational and Environmental Medicine* 38(3): 272–278; Crane *et al.*, 1997a; Crane *et al.*, 1997b; and Clapp 1997). NAS felt that what new information there is provides little evidence of a connection between testicular cancer and herbicide exposure. Several studies of military working dogs showed abnormal testicular pathology and a moderate excess of seminomas in dogs that had worked in Vietnam. However, NAS did not feel that these studies carried great weight in the absence of exposure data and without observed excesses in human populations. 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.

#### Leukemia

In VAO, NAS found evidence for a possible association between herbicide exposure and leukemia 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 Update 1996, NAS reviewed seven new studies. Six of these studies showed no association between herbicide exposure and leukemia or a nonsignificant elevated risk. One study, a mortality study of farmers, showed a significantly increased PCMR for leukemia but did not correlate the increased PCMR to suspected herbicide exposure and did not control for other confounding factors. (See 61 FR 41445 for study citations.)

In Update 1998, NAS again found that, generally, the evidence of an

association of leukemia with herbicide exposure came from studies of agricultural workers and a small subset of the Seveso cohort. A population-based case-control study of farm workers in northeastern Italy (Amadori D, Nanni O, Falcini F, Saragoni A, Tison V, Callea A, Scarpi E, Ricci M, Riva N, Buiatti E. 1995. Chronic lymphocytic leukaemias and non-Hodgkin's lymphomas by histological type in farming-animal breeding workers: a population case-control study based on job titles. *Occupational and Environmental Medicine* 52(6): 374-379.) found a high risk among farmers who are also involved in animal breeding (OR=1.8, 95% CI 1.2-2.6). However, analysis of the population broken down by the more frequent occupational categories showed no significantly high risk in any occupation. A survey of total and site-specific cancer incidence in male and female adults from 1959 to 1987 (Waterhouse D, Carman WJ, Schottenfeld D, Gridley G, McLean S. 1996. Cancer incidence in the rural community of Tecumseh, Michigan: A pattern of increased lymphopoeitic neoplasms. *Cancer* 77(4): 763-770.), as compared with site-specific cancer incidence rates reported by the Connecticut tumor registry, showed a significantly increased incidence of non-Hodgkin's lymphoma, Hodgkin's disease, and chronic lymphocytic leukemia. A nested case-control study of this group, using risk factor information documented prior to diagnosis, found that the RR of a family history of lymphoma, leukemia, or multiple myeloma was significantly increased among patients with lymphoproliferative neoplasms (OR=3.8, CI 1.5-9.8; p=.005). The follow-up of the Seveso population (Bertazzi et al., 1997) also suggested an increased risk, but the results were based on very limited data from one small subset of the whole cohort. Other studies, including occupational studies (Kogevinas et al., 1997; Ramlow et al., 1996), a study of agricultural workers (Gambini et al., 1997), and studies of Vietnam veterans (Dalager and Kang, 1997; Crane et al., 1997b), showed no increased risk or increases or decreases that were not significant.

An association of leukemia with herbicide exposure is biologically plausible, and the histological similarity of chronic lymphocytic leukemia with non-Hodgkin's lymphoma also suggests an association. Nonetheless, the overall evidence is too slight to warrant assigning leukemia to a higher category. 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.

#### **Abnormal Sperm Parameters and Infertility**

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. VAO 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 VAO 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 VAO. (See 59 FR 344 for study citations.)

In Update 1996, NAS reviewed one occupational study. 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.

In Update 1998, NAS reviewed two new studies that evaluated hormone, semen quality, and fertility endpoints in relation to potential dioxin exposure. The Ranch Hand study (Henriksen GL, Michalek JE, Swaby JA, Rahe AJ. 1996. Serum dioxin, testosterone, and gonadotropins in veterans of Operation Ranch Hand. *Epidemiology* 7(4): 352-357.) reported a relatively small decrease in testosterone in relation to increased dioxin level. A study of British Columbia sawmill workers (Heacock H, Hogg R, Marion SA, Hershler R, Teschke K, Dimich-Ward H, Demers P, Kelly S, Ostry A, Hertzman C. 1998. Fertility among a cohort of

male sawmill workers exposed to chlorophenolate fungicides. *Epidemiology* 9(1): 56-60.) found reduced fertility rates among exposed workers but could not consistently attribute this to chlorophenolate exposure. NAS again determined that uncertainty remained due to methodologic limitations of some existing studies.

NAS also reviewed the related fertility endpoint of altered sex ratio as a result of dioxin/herbicide exposure. One study of a small part of the Seveso population (Mocarelli P, Brambilla P, Gerthoux PM, Patterson DG Jr, Needham LL. 1996. Change in sex ratio with exposure to dioxin. *Lancet* 348(9024): 409.) suggested an altered ratio of male to female children, but other studies did not support that finding (Garry VF, Schreinemachers D, Harkins ME, Griffith J. 1996b. Pesticide applicators, biocides, and birth defects in rural Minnesota. *Environmental Health Perspectives* 104(4): 394-399; Heacock et al., 1998). NAS concluded that experimental animal evidence and further mechanistic data were needed to evaluate the relationship between sex ratio and exposure to dioxin or herbicides.

Accordingly, on the basis of all available evidence, 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.

#### **Motor/Coordination Dysfunction**

NAS indicated in VAO that it had found no significant studies available to analyze whether an association exists between herbicide exposure and motor/coordination dysfunction. In Update 1996, NAS reported finding no new studies directly addressing this topic. In Update 1998, NAS reported that it was not aware of new studies relating directly to 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 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. In VAO, NAS 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. VAO 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.)

In Update 1996, NAS 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 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 suggested that peripheral nerve problems were more prevalent in the exposed group. One of these studies 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 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 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. (See 61 FR 41446-47 for study citations.)

In Update 1998, NAS stated that no new information had appeared since Update 1996 to alter its previous conclusions on chronic persistent peripheral neuropathy. Where peripheral neuropathy is due to a toxic exposure (such as to herbicides), it is characterized by acute onset and subsequent resolution of the neuropathy after exposure to the toxin is terminated. It would not be expected to appear for the first time many years after exposure. Although the Secretary has previously found a positive association between herbicide exposure and such acute and subacute (transient) 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**

Metabolic and digestive disorders covered in this notice include hepatic enzyme abnormality, lipid abnormalities, and ulcers. In VAO, NAS found that two studies related to hepatic enzyme abnormality did not demonstrate an association with liver disease, and that 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 Update 1996, NAS reviewed the same studies 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. One study found a nonsignificant increase in liver disease among individuals exposed to dioxin, and another found no correlation between serum dioxin levels and

abnormalities in liver function tests. One new study was reviewed in Update 1996 concerning an association between herbicide exposure and lipid abnormalities that showed no substantial differences between the exposed and reference groups. The only new study reviewed in Update 1996 concerning a relationship between ulcers and exposure to herbicides showed no increases in the frequency of ulcers. (See 61 FR 41447 for study citations.)

The two major lipids are cholesterol and triglycerides. They are carried in the blood attached to proteins to form lipoproteins. Lipoproteins are classed according to their density: very low density lipoprotein (VLDL); intermediate-density lipoprotein (IDL); low-density lipoprotein (LDL, the so-called "bad" cholesterol particle); and high-density lipoprotein (HDL, the "good cholesterol" particle). Lipid concentrations play a major role in determining an individual's susceptibility to cardiovascular disease. Disorders of lipoprotein metabolism are usually characterized by abnormally high or low concentrations of lipoproteins. A number of factors may influence these concentrations. For example, when assessing the effects of herbicide exposure, obesity must be controlled for because it is a primary determinant of both triglyceride and TCDD concentrations.

The majority of new studies reviewed by NAS in Update 1998 do not suggest any effects in lipid or lipoprotein concentrations as a result of exposure to herbicide agents. A study of 641 Australian Vietnam veterans (O'Toole BI, Marshall RP, Grayson DA, Schureck RJ, Dobson M, Ffrench M, Pulvertaft B, Meldrum L, Bolton J, Vennard J. 1996b. The Australian Vietnam Veterans Health Study: II. Self-reported health of veterans compared with the Australian population. *International Journal of Epidemiology* 25(2): 319-330.), did find an increased frequency of elevated cholesterol compared to that expected from national Australian data (RR=3.0, 95% CI 1.3-4.7), but the health problems of these veterans were self-reported, and the data are difficult to assess with any degree of certainty. A follow-up of the Ranch Hand study participants (Air Force Health Study (AFHS). 1996. An epidemiologic investigation of health effects in Air Force Personnel Following Exposure to Herbicides. Mortality Update 1996. Brooks AFB, TX: Epidemiologic Research Division. Armstrong Laboratory. AL/AO-TR-1996-0068. 31 pp.) showed essentially no differences in the prevalence of high triglyceride



levels, low HDL concentrations, or high ratios of total cholesterol to HDL cholesterol between the Ranch Handers and the comparison group. Other studies (Calvert *et al.*, 1996; Ott and Zober, 1996) similarly indicate a negative or at best a weak association for prevalence of any abnormal lipid or lipoprotein concentrations.

In Update 1998, NAS reviewed a few credible studies reporting some increase in gastrointestinal disease possibly associated with exposure to herbicide agents. A mortality study of a cohort of workers exposed to pentachlorophenol (Ramlow *et al.*, 1996) showed a slight increase in overall digestive system disease. Increases were higher for gastric and duodenal ulcer specifically (SMR 3.6, CI 1.2–8.3; 15-year latency SMR 5.6, CI 1.8–13.0). Higher rates of digestive disease generally were seen in those exposed to higher PCP levels, but a significant decrease in the risk for ulcer was found at higher levels of exposure. Liver cirrhosis increased significantly with level of exposure, but alcoholism played a role in some of these cases and cannot, therefore, be discounted in the rest. In a study of the self-reported health status of Australian veterans (O'Toole *et al.*, 1996b), data indicated that the veterans reported ulcer and other digestive disease more frequently than did the control group. In these instances, however, the authors suggested that psychological stress due to combat may have been a causative factor and implied that high alcohol consumption played a role. Two studies of American Vietnam veterans (AFHS, 1996; Dalager and Kang, 1997) reported an increased incidence of digestive disease, particularly cirrhosis or other liver disease. Lack of data about alcohol consumption, however, makes this information difficult to assess. Other studies provide no evidence of an association of digestive system disease with exposure to herbicide agents. Some studies, in fact, suggest no association (*e.g.*, Bullman TA, Kang HK. 1996. The risk of suicide among wounded Vietnam veterans. *American Journal of Public Health* 86(5): 662–667.), which observed a significant decrease in deaths due to digestive disease among Vietnam veterans who had been hospitalized for wounds suffered in Vietnam.

After considering all evidence available, 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.

### *Diabetes Mellitus*

In both VAO and Update 1996, NAS placed metabolic and digestive disorders (including diabetes mellitus) in the category labeled "Inadequate/Insufficient Evidence to Determine Whether an Association Exists." According to NAS, this means that the available studies are of insufficient quality, consistency, or statistical power to permit a conclusion regarding the presence or absence of an association. For example, studies fail to control for confounding, have inadequate exposure assessments, or fail to address latency.

In Update 1998, NAS reviewed several new studies, including the 1997 report from the Ranch Hand study (Henrikson GL, Ketchum NS, Michalek JE, Swaby JA. 1997. Serum dioxin and diabetes mellitus in veterans of operation Ranch Hand. *Epidemiology* 8:252–258), that addressed the issue of diabetes mellitus. Based on the evidence reported in these and the previously reviewed studies, NAS again concluded that there is inadequate/insufficient evidence to determine whether an association exists between herbicide or dioxin exposure and increased risk of diabetes. However, since NAS released Update 1998 the National Institute of Occupational Safety and Health (NIOSH) published a report that detects an association, though not a strong association between diabetes and dioxin exposure. The study does suggest a dose response relationship because of excess cases of diabetes found in workers having the highest serum-lipid levels of dioxin (Calvert GM, Sweeney MH, Deddens J, Wall DK. 1999. Evaluation of Diabetes Mellitus, Serum Glucose and Thyroid Function Among U.S. Workers Exposed to 2,3,7,8 tetrachlorodibenzo-p-dioxin. *Occupational and Environmental Medicine* 56:270–276). The Secretary has concluded that the NIOSH study is potentially important enough that it warrants a full review by NAS as soon as possible, and he has directed VA to amend its contract with NAS for the third biennial update to require a special report on herbicide exposure and diabetes, as a separate deliverable, within approximately six months. The Secretary will make a determination as to whether there is an association between herbicide exposure and diabetes mellitus after NAS has reviewed the NIOSH report.

### **Immune System Disorders**

In VAO, NAS found 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 Update 1996 that no new studies of heightened susceptibility to infectious disease or new studies that investigated the association of autoimmune disease with exposure to herbicides had been identified. However, some new information had been published regarding the effects of TCDD on immunological parameters in laboratory measurements. The new studies 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. (See 61 FR 41447 for study citations.)

In Update 1998, NAS reviewed two new studies relating to the incidence of infectious diseases in American Vietnam veterans and two new studies of Australian Vietnam veterans. A proportionate mortality study of Vietnam veterans (Visintainer PF, Barone M, McGee H, Peterson EL. 1995. Proportionate mortality study of Vietnam-era veterans of Michigan. *Journal of Occupational and Environmental Medicine* 37(4): 423–428) studied a cohort of 377,028 veterans who are on the Michigan Department of Management and Budget's Vietnam-Era Bonus List. Vietnam veterans compared with non-Vietnam veterans had a slightly elevated proportionate mortality ratio from infectious and parasitic diseases (PMR=1.6, CI 1.2–2.1, N=56). The study, however, did not distinguish Vietnam veterans exposed to Agent Orange from those with no known exposure. Watanabe and Kang (1995) (Watanabe KK, Kang HK. 1995. Military service in Vietnam and the risk of death from trauma and selected cancers. *Annals of Epidemiology* 5(5): 407–12.) found a nonsignificant increased risk for infectious diseases in Vietnam Marines compared with non-Vietnam Marines (RR=2.8; CI 0.8–10.3). The studies of Australian Vietnam veterans did not show any increase in mortality due to infectious or parasitic diseases (Crane *et al.*, 1997a,b). NAS concluded that no evidence is available to associate defects in the immune response with Agent Orange exposure.

NAS also discussed several studies concerning exposure to halogenated aromatic hydrocarbons and shifts in lymphocyte subpopulations. It concluded on the basis of these studies that there is inadequate or insufficient evidence to determine whether an association exists between exposure to herbicides and immune suppression or autoimmunity.

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.

### Circulatory Disorders

NAS noted in VAO 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 in Update 1996 that showed no increase in the frequency of heart disease. Another study 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 of the data from an Air Force study provided 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. (See 61 FR 41447-48 for study citations.)

In Update 1998 NAS found sporadic reports of increased circulatory disease potentially related to exposure to herbicides or TCDD. A study of cancer

and circulatory system mortality among 1,189 male workers in a chemical plant in Hamburg, Germany (Flesch-Janys D, Berger J, Gurn P, Manz A, Nagel S, Waltsgott H, Dwyer JH. 1995. Exposure to polychlorinated dioxins and furans (PCDD/F) and mortality in a cohort of workers from a herbicide-producing plant in Hamburg, Federal Republic of Germany. *American Journal of Epidemiology* 142(11): 1165-1175.) found overall circulatory system disease mortality to be elevated among exposed workers. Results were dose-dependent; the RR among those exposed to the highest estimated levels of TCDD was 2.0 (95% CI 1.2-3.3). The increased risk appeared to be restricted to ischemic heart disease (IHD). Information was not available for confounding factors related to IHD, but the authors reasoned that the use of an unexposed referent population combined with the strong dose-response relationship argued against attributing the results to confounding factors. They also noted that the smoking rates and socioeconomic status of both cohorts appeared to be similar. In a simple random sample of Australian Army Vietnam veterans on self-reported health status (O'Toole *et al.*, 1996b), hypertension and other circulatory system disease were reported significantly more frequently by veterans. However, there was no significant association with combat exposure, and veterans were more likely to be current or former smokers and to report high alcohol consumption. The ongoing study of Ranch Hand veterans (AFHS, 1996), observed a significant increase of circulatory disorders among ground troops (SMR 1.5, CI 1.0-2.2), with nearly half of the increase due to atherosclerotic heart disease (SMR 1.4, CI 0.8-2.1). However, data on smoking and alcohol use were not available.

Most studies, however, noted decreases in incidence of circulatory disorders, or at best, nonsignificant increases among exposed individuals. NAS found inconsistent results across the studies reviewed. Interpretation of individual studies was generally limited by a lack of information on cigarette smoking, obesity, serum lipid levels, presence of diabetes, and other risk factors. Accordingly, after reviewing all available evidence, 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.

### Respiratory Disorders

In VAO, NAS examined studies that covered a wide variety of respiratory disorders other than respiratory cancers (*e.g.*, chronic bronchitis, asthma, pleurisy, pneumonia, and tuberculosis). 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.)

In Update 1996, NAS reviewed three new studies, all of which found no significant increase in respiratory disease associated with herbicide exposure. (See 61 FR 41448 for study citations.)

In Update 1998, NAS reviewed evidence from several new occupational and veteran studies (Becher *et al.*, 1996; Svensson *et al.*, 1995; Ott and Zober, 1996; Ramlow *et al.*, 1996; Kogevinas *et al.*, 1997; Bullman TA, Kang HK. 1996. The risk of suicide among wounded Vietnam veterans. *American Journal of Public Health* 86(5): 662-667; O'Toole *et al.*, 1996b; Watanabe and Kang, 1996; Dalager and Kang, 1997; Crane *et al.*, 1997a; Crane *et al.*, 1997b; and the ongoing study of Ranch Hand veterans, AFHS, 1996). O'Toole *et al.*, 1996b showed the strongest association between exposure and respiratory disease. Although there was no significant increase in overall respiratory system disease among veterans, hay fever, bronchitis, emphysema, and other respiratory disease were significantly elevated compared to the general population. However, these conditions were not related to an index of combat exposure, and the veterans were more likely to have smoked at some point in their lives than the general population. Although, in general, there were sporadic reports of increased respiratory disease potentially related to exposure to herbicides or dioxin, the results were inconsistent across the studies. In addition, interpretation of individual studies was generally limited by a lack

of information on cigarette smoking. 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.

#### Skin Cancer

In VAO, NAS 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 VAO.)

Update 1996 reviewed one new study (Lynge, 1993) that did find an excess risk of skin cancer. However, another new study found no increased risk of skin cancer. Three other new studies 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 found an increased PCMR for skin cancer in white male farmers. This 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. (See 61 FR 41448 for study citations.)

In Update 1998, NAS discussed malignant melanoma separately from squamous and basal cell carcinomas because of the different biologic behaviors and risk factors for these cancers.

#### Melanoma

Two new studies showed a statistically significant increase in melanoma mortality, but the data are not particularly strong. A study of U.S. Marine and Army veterans (Watanabe and Kang, 1996) found an increased risk of skin cancers only among Marine

veterans (PMR=1.3, CI 1.0–1.6). Army veterans showed no increased risk in comparison to any of the control groups. This study made no distinction between melanoma and other skin cancers. A study of Australian Vietnam veterans (Crane *et al.*, 1997a) showed an increased risk when compared to the Australian population, but no increased risk when the comparison group was non-Vietnam veterans (Crane *et al.*, 1997b). None of these studies controlled for exposure to sunlight, the greatest risk-factor for malignant melanoma. A study of Swedish fishermen (Svensson *et al.*, 1995) reported no elevated incidence of melanoma and found a decreased risk of death from the disease compared to the general Swedish population. Other new studies and updates of previous studies found either no increased risk or only a slightly elevated increase that was not considered significant (Bertazzi *et al.*, 1997; Kogevinas *et al.*, 1997; Hertzmann *et al.*, 1997; Dalager and Kang, 1997; Clapp, 1997). NAS did not feel that the evidence warranted altering its prior determination that there was inadequate or insufficient evidence of an association between exposure to herbicide agents and the subsequent development of malignant melanoma.

#### Basal Cell and Squamous Cell Carcinomas

The most compelling study reviewed by NAS was a Canadian community case-control study (Gallagher RP, Bajdik CD, Fincham S, Hill GB, Keefe AR, Coldman A, McLean DI, 1996. Chemical exposures, medical history, and risk of squamous and basal cell carcinoma of the skin. *Cancer Epidemiology, Biomarkers and Prevention* 5(6): 419–424.), which found an increased risk for squamous cell carcinoma, but not basal cell carcinoma, in individuals exposed to herbicides (OR=1.5, CI 1.0–2.3). The risk increased with increasing lifetime exposure. However, neither control for confounders nor assessment of exposure were adequate. Moreover, the findings in this study are in conflict with the earlier findings in the Ranch Hand study (Wolfe WH, Michalek JE, Miner JC, Rahe A, Silva J, Thomas WF, Grubbs WD, Lustik MB, Karrison TG, Roegner RH, Williams DE, 1990. Health status of Air Force veterans occupationally exposed to herbicides in Vietnam. I. Physical health. *Journal of the American Medical Association* 264: 1824–1831.) of an increased incidence of basal cell carcinoma, but not squamous cell carcinoma. The study of Swedish fishermen (Svensson *et al.*, 1995) showed a statistically significant increase in the incidence of such

cancers (RR=2.3, CI 1.4–3.5) among the fishermen who ate more of the fish potentially containing higher levels of organochlorine compounds. However, this study provided no measurements of the levels of TCDD or arsenic in either fish or fishermen. Other studies reviewed by NAS generally reported no statistically significant increases of basal cell or squamous cell carcinomas in exposed groups. Again, NAS did not feel that the evidence warranted altering its prior determination that there was inadequate or insufficient evidence of an association between exposure to herbicide agents and the subsequent development of basal cell and squamous cell carcinomas.

Accordingly, based on all available evidence, the Secretary has found that the credible evidence against an association between these skin cancers (malignant melanoma, basal cell carcinoma, and squamous cell carcinoma) and herbicide exposure outweighs the credible evidence for such an association, and he has determined that a positive association does not exist.

#### Cognitive and Neuropsychiatric Effects

NAS found in VAO 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.

Update 1996 reviewed one study 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 study of a large sample of Vietnam veterans 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, there continued to be no credible evidence for an association between herbicide exposure and cognitive disorders or neuropsychiatric

effects. (See 61 FR 41446 for study citations.)

In Update 1998, NAS briefly discussed a report from Australia (O'Toole BI, Marshall RP, Grayson DA, Schureck RJ, Dobson M, French M, Pulvertaft B, Meldrum L, Bolton J, Vennard J. 1996c. The Australian Vietnam Veterans Health Study: III. Psychological health of Australian Vietnam veterans and its relationship to combat. *International Journal of Epidemiology* 25(2): 331-340.) that analyzed the self-reported psychiatric states of Vietnam veterans as determined 20-25 years after the war. This study found higher prevalences of alcohol abuse or dependence, PTSD, and social and simple phobias among Vietnam veterans than among the civilian population. However, there was no attempt to relate these behavioral disorders to herbicide exposure. NAS stated it was unaware of other new studies that provide any further evidence of an association between herbicide exposure and cognitive or neuropsychiatric disorders. Therefore, based on available evidence, the Secretary continues to find that the credible evidence against an association between cognitive or neuropsychiatric disorders and herbicide exposure outweighs the credible evidence for such an association, and he has determined that a positive association does not exist.

#### **Reproductive Effects in Male Veterans**

In Update 1998 NAS, as it had in VAO and Update 1996, reviewed the current literature with respect to possible associations between herbicide exposure and various reproductive effects, *i.e.*, spontaneous abortion, spina bifida and other birth defects, neonatal/infant deaths and stillbirths, low birth weights, and childhood cancer in

offspring. NAS continued to find limited/suggestive evidence of an association of spina bifida with exposure to herbicides. For other reproductive outcomes, while the evidence suggests that an association is biologically plausible, various factors complicate reaching more definitive conclusions. (See Chapter 9 of the 1998 NAS report for additional information.)

Except in the case of spina bifida, compensation of a veteran or a veteran's child for these effects is beyond VA's statutory authority (title 38, United States Code) and would require enabling legislation. In 1996, § 421 of Public Law 104-204, as amended by § 404 of Public Law 105-114, gave VA the authority that the Secretary had requested to provide benefits for spina bifida in the natural children of individuals who had served in Vietnam during the period from January 9, 1962, through May 7, 1975. (See 38 U.S.C., Chapter 18.)

#### **Gastrointestinal Tumors and Brain Tumors**

In Update 1998 NAS, as it had in VAO and Update 1996, assigned gastrointestinal tumors (stomach cancer, pancreatic cancer, colon cancer, and rectal cancer) and brain tumors to the category labeled limited/suggestive evidence of no association with herbicide exposure. This category 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. NAS reviewed several new credible studies (see the 1998 NAS report, Chapter 7) concerning all of these conditions that generally showed no association or a negative association with herbicide exposure. One study of

workers exposed to TCDD in 1953 at a BASF plant in Germany (Ott and Zober, 1996) did report a statistically significant positive association of both death and incidence of digestive cancer. However, one of the cases of reported digestive cancer was actually primary liver cancer. If this had been classified as hepatobiliary cancer, the reported association probably would have been weaker. Accordingly, on the basis of all evidence available, the Secretary has found that the credible evidence against an association between gastrointestinal tumors (stomach cancer, pancreatic cancer, colon cancer, and rectal 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 1998." 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: October 26, 1999.

**Togo D. West, Jr.,**

*Secretary of Veterans Affairs.*

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