Gulf War and Health: Updated Literature Review of Depleted Uranium

Committee on Gulf War and Health: Updated Literature Review of Depleted Uranium

Board on Population Health and Public Health Practice

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CONCLUSIONS

In this chapter, the committee further evaluates the peer-reviewed published literature to draw conclusions about the long-term human health outcomes associated with exposure to natural uranium (as occurred in uranium-processing mills and other facilities and in residences) or depleted uranium (as occurred in the Gulf War). The discussion is organized according to cancer (or malignant) and noncancer (or nonmalignant) health outcome. Tables included at the end of this chapter contain results from the studies on which the committee bases its conclusions.

The traditional 5% level of statistical significance is used in describing the committee's conclusions regarding associations. Associations that did not reach the 5% level of statistical significance are described below as nonsignificant.

CANCER OUTCOMES

This section presents the strength of associations between exposure to natural or depleted uranium and particular cancer outcomes. It draws on the information from the many studies that were described in Chapter 7 and on *Gulf War and Health, Volume 1: Depleted Uranium, Pyridostigmine Bromide, Sarin, Vaccines* (IOM, 2000; hereafter referred to as *Volume 1*). The committee focused on the following sites: leukemias, lymphomas, and cancers of the lung, bone, kidney, bladder, stomach, central nervous system, prostate, and testis.

Most of the studies examined cancer mortality, but several studies of UK Gulf War veterans, Balkans veterans, and the Finnish drinking-water cohort also investigated cancer incidence. Because several cancers of interest are associated with a generally good chance of survival, cancer incidence (ascertainable from cancer-registration programs) is a better indicator of cancer risk than cancer-related mortality.

Results of cancer studies conducted in animal models are inconsistent (see Chapter 3). Several studies reported positive findings with respect to the development of a variety of cancers (including lung and renal cancers, leukemia, and sarcoma) in animals exposed by inhalation of uranium-ore dust or uranium dioxide, intratracheal injection of ^{235}U (as tetravalent or hexavalent uranium), or implantation of depleted-uranium pellets (Filippova et al., 1978; Hahn et al., 2002; Leach et al., 1973; Miller et al., 2005; Mitchel et al., 1999). However, other studies reported no increase in tumor development in animals exposed by inhalation of uranium-ore dust or ingestion of uranium (ATSDR, 1999; Cross et al., 1981; Maynard and Hodge, 1949).

Lung Cancer

Twenty-three studies of uranium-processing workers examined the association between exposure to uranium and lung cancer, as did three studies of military populations and three studies of residents (see Table 8-1). Four of the uranium-processing studies reported statistically significantly increased standardized mortality ratios (SMR) (that is, above 100). All four of those studies involved the same cohort of Oak Ridge, Tennessee, and all included employees of the Y-12 plant (see Table 8-2). The specific study populations overlapped, but each study took a different approach and examined a different timeframe. The most recent study of the cohort, by Richardson and Wing (2006), did not demonstrate a statistically significant increase in lung-cancer mortality in any dose stratum. However, when assessing the dose-response relationship with a 5-year lag assumption, they found a dose-response trend between external exposure and lung-cancer mortality (due largely to a small number of excess deaths among those who accumulated an external dose of 50 mSv or more) but did not find a similar trend for internal exposure. Analyses of the joint effects of external and internal exposures found that compared to the referent group (defined as less than 10 mSv external and internal dose), the rate ratio estimates were increased for each group defined by higher cumulative concentrations of internal and/or external dose; however, the results were not statistically significant and a dose-response trend was not observed. One major limitation of the uranium-processing worker studies is the lack of control for smoking, a major risk factor for lung cancer.

Contrary to the Y-12 cohort finding, a UK study of processors found significant reductions in both mortality from lung cancer (SMR, 85; $p < 0.05$) and incidence of lung cancer (standardized incidence ratio [SIR], 75; $p < 0.001$) but is limited by having only external-exposure data (McGeoghegan and Binks, 2000b). Beral et al. (1988) also reported a significant deficit in lung-cancer mortality (SMR, 64; $p < 0.01$) in employees of UK atomic-weapons research establishments with radiation records but found a significant positive association between cumulative exposure and lung-cancer mortality in a test for trend. One study of residents living near former nuclear-material processing plants found a significant reduction in risk of lung-cancer death (relative risk [RR], 0.95; 95% confidence interval [CI], 0.93-0.98) (Boice et al., 2003b); this study is limited by imprecise and incomplete data on exposure and information on risk factors.

Ritz et al. (1999) found a weak dose-response relationship with a 15-year lag per 100 mSv of external dose in workers in a uranium-processing plant. Cragle et al. (1988) reported a nonsignificant increase in lung cancer mortality (8 deaths) for salaried and hourly nuclear-fuels production-plant workers (SMR 152) but lower SMRs (also nonsignificant) for only hourly or only salaried workers. The study lacks exposure data. Pinkerton et al. (2004) reported a statistically nonsignificant increase in lung cancer mortality among uranium millers (SMR, 113; 95% CI, 89-141 compared to US referent rates) that was not found in earlier studies of this cohort. When compared to regional referent rates, the increase reached statistical significance (SMR, 151; 95% CI, 119-189). This study is limited by lack of assessment of individual exposure to uranium and other substances in the milling environment.

In summary, there is no consistent evidence of an effect of exposure to natural or depleted uranium on lung-cancer incidence in the studies reviewed. The finding is unchanged when one considers evidence from the studies with the strongest designs, for example, with measurement of cumulative exposure at the individual level, internal controls, a large study

population, long followup, and controlling for confounders. The pattern among studies is varied: some studies show increases in risk of lung cancer, and others show decreases. A major shortcoming of the studies is the lack of individual data on smoking, a primary risk factor for lung cancer.

The committee concludes that there is inadequate/insufficient evidence to determine whether an association between exposure to uranium and lung cancer exists.

This conclusion on lung cancer differs from the one in *Volume 1*. The previous committee concluded that there is limited/suggestive evidence of *no* association between exposure to uranium and lung cancer at cumulative internal doses lower than 200 mSv and that there is inadequate/insufficient evidence to determine whether an association between exposure to uranium and lung cancer exists at higher cumulative exposure (> 200 mSv). The present committee did not place quantitative limits on the dose for the following reasons:

- There is substantial uncertainty in the measurement of uranium exposure in the studies reviewed.
- The types of quantitative measure vary widely from study to study, from individual biomonitoring data to external or internal exposure measurements (often lacking data on many study subjects) to group estimates based on job title to a general category of years of employment. Furthermore, different dose-reconstruction methods were used to estimate dosage, and different cut-points were often used to categorize the dose in the data analysis, so it was difficult to draw a conclusion.
- Some studies of lung cancer that reported dose had small samples and often did not adjust for risk factors, such as smoking.

Because inhaled uranium dust remains in lung tissues and hilar lymph-node tissues for several years, they are potential targets for uranium radiation. Furthermore, lung cancer is a common malignancy and the leading cause of cancer death; even a modest effect could result in a meaningful increase in the number of cases of lung cancer (that is, an increase in an exposed group compared to an unexposed group might be detectable given the frequency of lung cancer occurrence). Therefore, the committee assigns high priority to continuing to monitor a possible association between exposure to depleted uranium and lung cancer.

Leukemias

The results of only one of the 23 studies reviewed by the committee achieved statistical significance: a residential study by Boice et al. (2003b) (see Table 8-3). The authors reported a reduction in mortality from leukemia (RR [computed by comparing SMRs from the study counties with control counties], 0.91; 95% CI, 0.86-0.97). However, that study is limited by a lack of exposure data and information on other risk factors. The remaining 22 studies showed both increases and decreases in risk associated with exposure to uranium, all of which were nonsignificant. There was no consistent evidence of effect, and the pattern among studies was highly varied. The same pattern was observed after restriction of consideration to the "larger studies" (those with a sample population of about 10,000 or more or with more than 10 cases).

The committee concludes that there is inadequate/insufficient evidence to determine whether an association between exposure to uranium and leukemias exists.

Leukemia is a relatively uncommon malignancy, so large study populations are generally needed to demonstrate any significant moderate effects. The studies reviewed by the committee generally did not have adequate sample size. Earlier studies were complicated by the broad grouping of and changes in classification for leukemia. On the basis of the evidence to date, the committee would assign a low priority to additional study of an association between exposure to depleted uranium and leukemias.

Lymphomas

This section includes discussion of two types of lymphoma: Hodgkin lymphoma (also known as Hodgkin's disease) and non-Hodgkin lymphoma (NHL). The risk of lymphatic malignancy is of particular interest because uranium is known to accumulate in lymph-nodel tissues. Study results are summarized in Tables 8-4 and 8-5.

Hodgkin Lymphoma

The studies considered (see Table 8-4), split virtually evenly between showing an increase in risk of Hodgkin lymphoma associated with exposure to natural or depleted uranium and showing no change or a decrease in risk of Hodgkin lymphoma associated with uranium exposure. The same pattern was observed after restriction of consideration to the "larger studies" (those with a sample population of about 10,000 or more or with more than 10 cases). Only the study by Nuccetelli (2005) achieved a statistically significant finding, showing a significant increase in the risk of Hodgkin lymphoma. Most of the smaller studies show nonsignificantly decreased risk of incidence or death.

Non-Hodgkin Lymphoma and Other Lymphatic Cancers

Table 8-5 presents the results of 24 published studies of a possible relationship between exposure to natural or depleted uranium and NHL. Most of them showed that exposed subjects experienced a risk of NHL equal to or lower than that in unexposed subjects. The same is true if one considers only the larger studies. One study indicated a significant increase in risk: the study by Archer (1973), which had a sample size of only 662, including four cases of lymphatic cancer.

The committee concludes that there is inadequate/insufficient evidence to determine whether an association between exposure to uranium and lymphomas exists. This conclusion applies to both Hodgkin lymphoma and non-Hodgkin lymphoma.

On the basis of the available evidence, the committee concludes that there is a lack of strong and consistent evidence of an association between uranium exposure and lymphatic cancers. The finding is unchanged when one considers evidence from the studies with larger samples and stronger designs: there is no consistent evidence of effect. The pattern among studies is highly varied, as one would expect if there truly were no effect in the population. Although the available evidence does not justify further consideration of a possible association between depleted uranium and lymphatic cancers, the committee concludes that further study of

this type of cancer may be warranted on biologic grounds, given that uranium is known to accumulate in the lymph nodes.

Bone Cancer

Twelve studies of uranium-processing workers, one study of a deployed population, and two residential studies assessed bone-cancer outcomes. In most of the studies, the risk of bone cancer was the same or decreased after exposure to natural or depleted uranium (see Table 8-6). Only one study had a significant finding: a statistically significant increase in bone-cancer incidence—four cases—in a Danish military population deployed to the Balkans (SIR, 600; 95% CI, 160-1530) (Storm et al., 2006). However, because three of the four cases occurred within the first year after deployment, it is unlikely that deployment-related exposure was a factor, given the latency of cancer. After lagging 1 year after deployment, bone-cancer incidence dropped to one case, with a nonsignificant SIR of 170 (95% CI, 0-1010).

The committee concludes that there is inadequate/insufficient evidence to determine whether an association between exposure to uranium and bone cancer exists.

Overall, the available studies do not provide clear and consistent evidence of an association between natural or depleted uranium and bone cancer. The estimated effects vary greatly from study to study, showing decreased risk, the same risk, or higher risk after exposure. Given that bone cancer is a relatively uncommon malignancy, relatively large study populations are generally needed to demonstrate any significant moderate effects. The studies reviewed by the committee generally did not have adequate sample size. On the basis of the available evidence, the committee would assign a low priority to additional study of an association between exposure to depleted uranium and bone cancer.

Renal Cancer

The committee considered 20 studies of an association between natural or depleted uranium and renal cancer. None of the published results demonstrated a significant increase in risk after uranium exposure (see Table 8-7). The reported SMRs, SIRs, and RRs varied above and below unity except for one residential study (Boice et al., 2003c), which indicated a statistically significant decrease in renal-cancer mortality associated with uranium exposure (RR, 0.58; $p < 0.05$). That study did not include exposure assessment or information on other risk factors. In a more detailed analysis, Dupree-Ellis and colleagues (2000) examined a possible dose-response relationship and found an increasing trend, driven primarily by four renal-cancer deaths in the highest-dose group (excess risk, 10.5/mSV; 90% CI, 0.6-57.4). That result was not statistically significant.

The committee concludes that there is inadequate/insufficient evidence to determine whether an association between exposure to uranium and renal cancer exists.

None of the 20 studies considered by the committee demonstrated a significant increase in risk of renal cancer after exposure to uranium. When attention was restricted to the studies with the largest samples, there was no positive evidence of an effect at the low exposures observed in the studies. On the basis of the available evidence, the committee would assign a low

priority to further study of an association between exposure to depleted uranium and renal cancer.

Bladder Cancer

The committee evaluated 20 published studies of a potential association between exposure to natural or depleted uranium and bladder cancer: 14 uranium-processing studies, two studies of military populations, and four residential studies (see Table 8-8). Most of the studies reported the same or reduced bladder-cancer mortality or incidence in exposed subjects. Only one finding achieved statistical significance: a UK processing study found a significant reduction in bladder-cancer incidence (SIR, 76; $p < 0.05$) but roughly equal mortality (SMR, 92; nonsignificant) (McGeoghegan and Binks, 2000b). That study is limited by a lack of data on internal radiation exposure and other risk factors. Two studies of veterans deployed to the Balkans reported increased but nonsignificant SIRs for bladder cancer, but both studies were based on very small numbers of observed cases (Gustavsson et al., 2004; Storm et al., 2006).

The committee concludes that there is inadequate/insufficient evidence to determine whether an association between exposure to uranium and bladder cancer exists.

Overall, the committee finds little evidence that exposure to natural or depleted uranium increases the risk of bladder cancer. Most of the studies, whether small or large, show the same or reduced risk of bladder cancer in people exposed to uranium. Although the two studies of deployed populations showed nonsignificant increases in risk, the estimates were based on small numbers of cases—two and seven. A small number of cases renders findings less robust in that changes in exposure or outcome status in only one or two people could have altered the findings substantially, so confidence in the findings is reduced. The committee would assign a low priority to further study of an association between exposure to depleted uranium and bladder cancer.

Brain and Other Central Nervous System Cancers

Findings of 20 published studies of an association between uranium exposure and brain and other central nervous system cancers are described in Table 8-9. Almost all failed to demonstrate statistically significant associations between uranium exposure and brain and other central nervous system cancers, but they are roughly evenly split between those showing increases in and those showing the same or decreases in mortality or incidence. That overall pattern is unchanged if one restricts attention to the larger or better designed studies. Only two studies had significant results: significant decreases in risk after uranium exposure. The study by Cragle et al. (1988) reported a statistically significant decrease in mortality after exposure in hourly workers at a nuclear-fuels production facility (SMR, 23; $p < 0.05$). However, the SMRs for salaried workers and for combined hourly and salaried workers were not statistically significant. In addition to a possible healthy-worker effect, the study may be limited by a lack of detailed exposure assessment and the use of "hourly" vs "salaried" as a proxy for socioeconomic status. Beral et al. (1988) also reported a significant deficit in mortality from brain and other nervous system cancers in processing workers (SMR, 32; $p < 0.05$).

The committee concludes that there is inadequate/insufficient evidence to determine whether an association between exposure to uranium and cancers of the central nervous system, including brain cancer, exists.

The published studies show inconsistent results that do not lead to a conclusion of an association between natural or depleted uranium and cancers of the central nervous system. Studies of some other cancers (for example, bladder cancer) showed an equal or reduced risk after exposure, but the distribution of studies of brain and other central nervous system cancers is more balanced: results are roughly equally divided between studies that show increased risk and studies that show the same or decreased risk. Because of that pattern, the committee believes that further study of an association between depleted uranium and central nervous system cancers may be warranted but should not be assigned a high priority.

Stomach Cancer

The committee considered 21 published studies of a possible association between natural or depleted uranium and stomach cancer, including 16 processing studies, one study of military populations, and four residential studies (see Table 8-10). All but three had statistically nonsignificant results, and most demonstrated the same or decreased mortality or incidence. The pattern is unchanged if one restricts consideration to the larger or better designed studies. The three studies that had statistically significant results all showed a decrease in mortality or incidence (McGeoghegan and Binks, 2000b; Dupree-Ellis et al., 2000; Beral et al., 1988). McGeoghegan and colleagues found a significantly decreased risk of stomach cancer (SIR, 76; $p < 0.05$) but an approximately equal risk of stomach-cancer death (SMR, 92; nonsignificant) in workers at the Springfields uranium-production facility (McGeoghegan and Binks, 2000b); however, the study is limited by inadequate data on exposure, particularly internal exposure.

The committee concludes that there is inadequate/insufficient evidence to determine whether an association between exposure to uranium and stomach cancer exists.

Overall, the committee finds little evidence to suggest that exposure to natural or depleted uranium increases the risk of stomach cancer. Most of the studies showed similar or reduced risk of stomach-cancer death and incidence in people exposed to uranium. Although four uranium-processing studies showed nonsignificant increase in SMRs, the findings were based on 15 or fewer cases. Similarly, the study of Danish deployed populations that showed a nonsignificant increase in risk was based on two cases. Therefore, confidence in the findings is low. In the view of the committee, further study of an association between depleted uranium and stomach cancer would have a low priority.

Male Genital Cancers

Prostatic cancer is the most frequently diagnosed cancer in men in the United States, and any increase in risk could result in a large increase in the number of cases or deaths. Testicular cancer, the most common cancer among young men, is of special interest to Gulf War veterans, and some studies of veterans suggested a higher but nonsignificantly increased risk (IOM, 2006).

Prostatic Cancer

The committee evaluated 19 published studies of a potential association between exposure to natural or depleted uranium and prostatic cancer, including 14 processing studies, two studies of deployed populations, and three residential studies (see Table 8-11). Only one reported a statistically significant finding: McGeoghegan and Binks (2000b) found a significant reduction in prostatic-cancer incidence (SIR, 77; $p < 0.05$) but not mortality (SMR, 89; nonsignificant) in workers at the Springfields uranium-processing plant. The study is limited by the lack of data on internal radiation exposure. Three other studies of processing workers reported increased prostatic-cancer mortality, but none of the SMRs was statistically different from the null value indicating no effect (Ritz, 1999; Beral et al., 1988; Loomis and Wolf, 1996).

The larger studies (those with samples of about 10,000 or more or with more than 10 affected cases) had more findings of decreased risk than of increased risk in those exposed to uranium. No study showed a statistically significant increase in risk. The only statistically significant finding was a decrease in cancer incidence (SIR, 77; $p < 0.05$). Overall, there is little evidence of an association between uranium exposure and prostatic cancer.

The committee concludes that there is inadequate/insufficient evidence to determine whether an association between exposure to uranium and prostatic cancer exists.

Of the 19 studies considered, none demonstrated a significantly increased risk of prostatic cancer after exposure to uranium, and one showed a significant decrease in cancer incidence but not mortality. If only the studies with the largest samples are considered, the committee finds that there is no affirmative evidence of effect. On the basis of the available evidence, the committee would assign a low priority to further study of an association between exposure to depleted uranium and prostatic cancer.

Testicular Cancer

Table 8-12 summarizes the findings of 15 published studies considered by the committee for a possible relationship between exposure to natural or depleted uranium and testicular cancer, including 11 studies of uranium-processing workers, three studies of military populations, and one study of residents living near a nuclear facility in Pennsylvania. None of the results achieved statistical significance. All studies of processing workers showed reduced testicular-cancer mortality in people exposed to uranium but did not reach the 5% level of statistical significance. All three studies of deployed veterans found increased incidence rate ratios or SIRs, but they also did not reach statistical significance (Macfarlane et al., 2003; Gustavsson et al., 2004; Storm et al., 2006).

The committee concludes that there is inadequate/insufficient evidence to determine whether an association between exposure to uranium and testicular cancer exists.

The committee finds no consistent evidence that uranium exposure increases the risk of testicular cancer. All occupational cohorts had lower mortality. Testicular cancer, although very rare in the general population, is common in young adults and therefore prevalent in deployed veterans. The nonsignificant excess in incidence observed in the studies of military populations could be due in part to routine medical surveillance of the deployed veterans. Despite the inconsistent evidence, testicular cancer is of special interest to Gulf War veterans. The

committee believes that further study of an association between depleted uranium and testicular cancer may be warranted but should not be assigned a high priority.

Other Cancers

A study of health outcomes in 53,462 Gulf War veterans reported only all-cancer incidence, not site-specific incidence (Macfarlane et al., 2005). It did not find a statistically significant increase in cancer incidence (mortality rate ratio, 1.01; 95% CI, 0.79-1.30). However, the 13-year followup period may be too short for most cancers to have developed.

Early studies by Archer (1973), Wagoner et al. (1964), and Waxweiler et al. (1983) combined hematopoietic and lymphopoietic cancers, but only one (that by Archer) found a significant increase (SMR, 392; $p < 0.05$). Beral et al. (1988) also found a significantly lower RR of all lymphopoietic and hematopoietic cancers (RR, 0.46; 95% CI, 0.23-0.94) in workers with radiation-exposure records than in those without exposure records.

NONCANCER OUTCOMES

The following subsections present the strength of the evidence of associations between exposure to natural or depleted uranium and specific nonmalignant health outcomes. They draw on the information from the many studies that were described in Chapter 7 and *Volume 1*. The committee has highlighted the relevant findings on nonmalignant outcomes from the literature, with a focus on outcomes related to the organs and organ systems likely to be affected by natural or depleted uranium, such as the kidneys and the respiratory, central nervous, and reproductive systems. The findings show both positive and negative associations between uranium and nonmalignant health outcomes.

Nonmalignant Renal Disease

Mortality

Fourteen studies assessed the association between occupational exposure and renal-disease mortality. Four reported an excess in mortality that was not statistically significant (see Table 8-13). Two of those followed the mortality experience of uranium millers in the Colorado Plateau region. In 1983, Waxweiler and colleagues reported an excess in deaths from chronic nephritis (SMR, 167; 95% CI, 60-353). However, all deaths in the group occurred in short-term workers, and this lessened the likelihood that the deaths were related to uranium exposure (IOM, 2000). In a followup study of the Colorado group, Pinkerton and colleagues also observed an increase in mortality due to chronic renal disease (SMR, 135; 95% CI, 58-267) (Pinkerton et al., 2004) that was not statistically significant. Similarly, Dupree-Ellis and colleagues (2000) found an excess in mortality from chronic nephritis (SMR, 188; 95% CI, 75-381) in workers at the Mallinckrodt Chemical works plant that was not statistically significant. The authors noted that prior exposure to silica in previous jobs and misclassification of renal diseases may have limited the interpretability of their results. McGeoghegan and Binks (2001) found a nonsignificant increase in deaths due genitourinary diseases in radiation workers compared with the English and Welsh populations (5 observed vs 4.63 expected; SMR, 108) in a study of processors at the British Nuclear Fuels Chapelcross site.

Cragle and colleagues (1988) reported statistically significantly fewer deaths due to genitourinary diseases in hourly employees (SMR, 39; 95% CI, 10-96) in a study of workers at the Savannah River plant. McGeoghegan and Binks (2000b) also reported significantly fewer deaths than expected in radiation workers (SMR, 57; $p < 0.01$). Frome and colleagues (1997) reported fewer deaths than expected from diseases of the genitourinary system (SMR, 83) in white men in a study of processing workers at the four Federal nuclear plants in Oak Ridge, Tennessee. An earlier study of Oak Ridge workers at the Y-12 and K-25 uranium-enrichment facilities revealed no difference between the numbers of observed and expected deaths from chronic nephritis (SMR, 99; 95% CI, 71-126[1]) (Frome et al., 1990), as reported in *Volume 1*. The observed findings were probably influenced by a healthy-worker effect.

In many of the 14 studies, the computed death rates included all genitourinary conditions instead of focusing on renal diseases. Despite reported increases in observed deaths, the SMRs may not have reflected a true response to uranium exposure. In several of the plants, uranium exposure coexisted with other relevant heavy-metal or chemical exposure. Generally, most researchers were unable to isolate the effects of uranium exposure alone.

Morbidity

Gulf War Veterans Depleted-Uranium Surveillance Study

McDiarmid and colleagues conducted a medical investigation of Gulf War veterans who inhaled or ingested airborne depleted-uranium particles or experienced depleted-uranium wound contamination as a result of friendly-fire incidents and found renal-function measurements that were generally within normal clinical limits (see Table 8-14) (McDiarmid et al. 2000; 2001; 2004; 2006; 2007). Urinary uranium excretion was used in the exposure assessment, and subjects were separated into high- and low-exposure groups on the basis of a cutpoint of 0.10 µg/g of creatinine. In the first of the Baltimore Veterans Affairs Medical Center (BVAMC) studies, veterans with retained depleted-uranium shrapnel fragments had higher urinary uranium concentrations than those without 7 years after first exposure. Urinary uranium ranged from 0.01 to 30.74 µg/g of creatinine in veterans with retained fragments and 0.01 to 0.05 µg/g creatinine in veterans without fragments. Despite that finding, renal-function measures (serum creatinine, beta-microglobulin, retinol-binding protein, serum uric acid, urinary creatinine, and urinary protein) were quite similar between the high- and low-exposure groups (McDiarmid et al., 2000). In the 1999 evaluation, urinary uranium ranged from 0.018 to 39.1 µg/g of creatinine in the depleted-uranium–exposed veterans with retained fragments and 0.002 to 0.231 µg/g of creatinine in depleted-uranium–exposed veterans without fragments. Clinical tests revealed renal measures within normal limits with slight differences between high- and low-uranium groups. The authors did not detect any clinically important changes in renal function due to depleted-uranium exposure; urinary creatinine concentration was slightly lower in the high-uranium group, but the difference was only marginally significant (McDiarmid et al., 2001). An increase in urinary uranium (24-hour urinary uranium concentrations higher than 0.05 µg/g of creatinine) was seen in four of the 30 newly enrolled veterans (McDiarmid et al., 2002). The 2001 surveillance reported urinary uranium ranging from 0.001 to 78.125 µg/g of creatinine. The presence of retained depleted-uranium shrapnel appeared to be associated with higher urinary uranium concentration. In addition, most urinary-uranium results were consistent over time.

[1]The confidence interval was calculated by the Committee on Health Effects Associated with Exposure During the Gulf War; it was not stated in the original study (IOM, 2000).

Mean values of all renal-function markers were within normal clinical limits with few statistically significant differences between high- and low-uranium groups 10 years after first exposure. Serum creatinine was higher in the low-uranium group (0.85 vs 0.95 mg/dL; $p = 0.03$), and urinary retinol-binding protein (65.58 vs 46.13 µg/g of creatinine; $p = 0.06$) and total urinary protein (78.69 vs 54.63 mg/g of creatinine; $p = 0.01$) were higher in the high-uranium group (McDiarmid et al., 2004). Those differences were not observed in the previous evaluations of this group. In 2003, all but one of the renal measures was within normal clinical limits. The difference in serum phosphate concentration was the only measurable difference between the high- and low-exposure groups (4.11 vs 3.75 mg/dL; $p = 0.03$) (McDiarmid et al., 2006), but its clinical importance is unclear.

In the most recent evaluation, urinary uranium ranged from 0.002 to 44.1 µg/g of creatinine in total 24-hour urine, and participants with known embedded depleted-uranium shrapnel fragments and specific uranium indicators of depleted uranium had concentrations at or above the cutpoint of 0.10 µg/g of creatinine. The results showed a high correlation between current and cumulative uranium-exposure measures. Of the 34 veterans with depleted-uranium shrapnel, 10 had current urinary uranium concentrations that exceeded the cutpoint of 0.10 µg/g of creatinine. The same number had cumulative urinary uranium concentrations over the cutpoint of 10 µg/g of creatinine. Differences in mean serum uric acid were borderline ($p = 0.03$) when groups with high and low cumulative uranium exposure were compared. Despite that finding, the values were within the normal clinical range, and the differences were small: 5.22 mg/dL in the high group and 6.19 mg/dL in the low group. Other renal characteristics had no significant differences whether current or cumulative uranium measures were used (McDiarmid et al., 2007).

Drinking Water and Residential Exposure

Kurttio and colleagues investigated renal measures related to uranium exposure through drinking water in 325 Finnish people who obtained their water from drilled wells (see Table 8-14). The 2002 report on the cohort noted a statistically significant association between uranium exposure and calcium excretion ($p = 0.03$) in well-water users (Kurttio et al., 2002). The authors documented an association between urinary uranium and fractional excretion of calcium for all exposure metrics. They also observed a statistically significant association between urinary uranium and fractional phosphate ($p = 0.03$). There was no association between uranium exposure and measures of glomerular function (Kurttio et al., 2002).

In a later study of the cohort, Kurttio and colleagues (2006a) found that urinary uranium concentrations were an average of 44% greater than during prior sampling. The study further examined renal toxicity due to uranium exposure through drinking water in 193 of the 325 people included in the 2002 study. In general, markers of renal function were within normal limits. Biomarkers of cytotoxicity, renal proximal tubular function, glomerular function, and other exposure indicators were not significantly associated with urinary uranium concentration. However, there were statistically significant associations between cumulative uranium intake and glucose excretion ($p = 0.02$) and between uranium exposure and increased blood pressure (diastolic, $p = 0.01$; systolic, $p = 0.07$).

In the only study that examined an association between residential exposure and renal effects, researchers observed a statistically significant excess in renal disease (standardized prevalence ratio [SPR], 215; 99% CI, 186-248) and bladder disease (SPR, 132; 99% CI, 111-

156) in people who lived near the Fernald Feed Materials Production Center (FFMPC) in Ohio. The outcomes included increases in a few subcategories, such as kidney stones (SPR, 398; 99% CI, 336-468) and chronic nephritis (SPR, 203; 99% CI, 76-435). However, the health outcomes were self-reported, and some were not verified, so the potential for outcome misclassification was increased. Residents who obtained their drinking water from a well or cistern had higher urinary microalbumin concentrations (Pinney et al., 2003).

Occupational Uranium Exposure

Boiano and colleagues conducted a medical investigation of workers at the FFMPC (see Table 8-14). They observed urinary uranium concentrations up to 13 µg/L, and 109 of the participants had concentrations under the detection limit of 5 µg/L. However, no associations were observed between measures of uranium exposure and glomerular filtration or tubular markers (Boiano et al., 1989).

A study of processors in Egypt (Shawky et al., 2002) found a mean urinary uranium concentration of 17.8 µg/L. It also reported that urinary uranium was increased in the 13 participants who provided spot urine specimens, ranging from 8 to 29 µg/L. There was a correlation between urinary uranium and serum creatinine in the 13 specimens, and mean uranium excretion was more than 20 times the occupational-exposure decision level of 0.8 µg/L. However, there were no individual exposure data other than data on the 13. That, in addition to the small sample and the absence of more specific markers for evaluating tubular dysfunction, limits the value of the reported results.

Conclusion

Although high exposure to uranium, a heavy metal, is known to be toxic to the kidneys (see Chapter 3 for a discussion of the toxicity of uranium in animal models), the literature evaluated does not provide substantial evidence of an association between exposure to natural or depleted uranium and important clinical renal effects in humans. Several studies found slight changes in renal markers but no abnormalities in renal function. Gulf War veterans exposed to depleted uranium in embedded shrapnel had minor changes in renal measures and increased urinary uranium concentrations over the course of a 14-year followup, but overall mean values remained within normal clinical ranges. The studies of well-water users in Finland thoroughly characterized the nature of exposure but examined renal effects in a small group and included a relatively short followup. Studies of workers in processing plants at the Fernald Feed Materials Production Center detected no association between uranium exposure and glomerular or tubular markers.

The committee concludes that there is inadequate/insufficient evidence to determine whether an association between exposure to uranium and nonmalignant renal disease exists.

This conclusion on renal disease differs from the one in *Volume 1*. The previous committee concluded that there is limited/suggestive evidence of *no* association between exposure to uranium and clinically significant renal dysfunction. On the basis of the available evidence, the present committee could not rule out renal effects after exposure of any magnitude (see Chapter 4 for the definition of the category of limited/suggestive evidence of *no* association). The committee also could not place quantitative limits on the dose, for reasons similar to those detailed above in connection with lung cancer.

The published research evidence is inadequate to support a conclusion about depleted uranium as a cause of nonmalignant renal disease. The well-observed renal effects of heavy metals that are excreted in urine make a deleterious effect of depleted-uranium exposure plausible if the exposure is of sufficient magnitude and duration. The kidneys are identified as the most sensitive target of uranium toxicity in the US Army's "Capstone Report" (USACHPPM, 2004) and in the National Research Council report, *Review of Toxicologic and Radiologic Risks to Military Personnel from Exposure to Depleted Uranium During and After Combat* (NRC, 2008). However, available modes of uranium exposure—industrial exposure, groundwater exposure, and depleted-uranium exposure of a small number of veterans—do not indicate renal toxicity in these settings. Additional studies of larger numbers of exposed people with well-characterized exposure and renal outcomes will be needed before any definitive conclusions can be drawn about a nephrotoxic effect of exposure to depleted uranium in a war theater. On the basis of the available evidence, the committee would assign a high priority to further study of an association between exposure to depleted uranium and nonmalignant renal disease.

Nonmalignant Respiratory Disease

The committee evaluated 14 mortality and two morbidity studies of exposure to uranium and nonmalignant respiratory disease (see Tables 8.15 and 8.16). In a 2004 study of a cohort of uranium millers in the Colorado Plateau, Pinkerton and colleagues (2004) observed a significant increase in mortality from nonmalignant respiratory disease compared with the US referent population (SMR, 143; 95% CI, 116-173) due to an excess in mortality from emphysema (SMR, 196; 95% CI, 121-299) and pneumoconioses and other respiratory diseases (SMR, 168; 95% CI, 126-221). Those findings were consistent with those of a previous study of the cohort (Waxweiler et al., 1983). However, mortality from emphysema was higher in workers employed before 1955, when exposures to silica and vanadium, in addition to exposure to uranium, were thought to be at their highest (before 1995: 17 observed; SMR, 222; 95% CI, 129-356; 1955 or later: 4 observed; SMR, 130; 95% CI, 36-333) (Pinkerton et al., 2004). Frome and colleagues (1990) also reported a significant excess in deaths from nonmalignant respiratory diseases. However, several studies found decreases in lung-disease mortality. As reported in *Volume 1*, Ritz and colleagues (1999) found a significant decrease based on 53 deaths. As with mortality from nonmalignant renal diseases, the respiratory-disease outcomes were grouped, so the ability to observe effects of individual diseases was reduced. In addition, the issue of exposure to multiple respiratory toxicants is important with respect to respiratory disease: many workers were often exposed to other agents (such as silica) known to have effects on the lungs.

In a study of lung disease in workers at the FFMPC, investigators found some associations between indicators of uranium exposure and respiratory effects. The ratio of 1-second forced expiratory volume (FEV_1) to forced vital capacity was associated with the job-history–derived uranium-exposure index after adjustment for smoking. However, the FEV_1 alone was not associated with the exposure index. Shortness of breath was significantly associated with self-reported uranium exposure (Boiano et al., 1989). People who lived close to the plant had significantly fewer cases of asthma (SPR, 85; 99% CI, 73-98), chronic bronchitis (SPR, 19; 99% CI, 14-24), and emphysema (SPR, 61; 99% CI, 41-68) compared with National Health Interview Survey rates (Pinney et al., 2003).

The committee concludes that there is inadequate/insufficient evidence to determine whether an association between exposure to uranium and nonmalignant respiratory disease exists.

Results of several of the studies support an effect of employment in uranium-processing facilities on nonmalignant respiratory disease, but their applicability to military depleted-uranium exposure is limited by the extent of concomitant coexposure of such workers to other respiratory toxicants (such as silica, asbestos, and vanadium). Results of inhalation studies of various forms of uranium in several animal species are inconsistent with respect to nonmalignant respiratory effects (see Chapter 3). On the basis of the available evidence, the committee would assign a high priority to further study of an association between exposure to depleted uranium and nonmalignant respiratory disease.

Neurologic Effects

The studies of uranium-processing workers showed no excess in neurologic-disease mortality (Cragle and et al., 1988; Dupree-Ellis et al., 2000; Frome et al., 1990; 1997; McGeoghegan and Binks, 2000a; b; 2001; Boice et al., 2006; Polednak and Frome, 1981) (see Table 8-17). As part of the Depleted Uranium Follow-up Program at the BVAMC, McDiarmid and colleagues used various traditional and automated test batteries (see Chapter 7) to assess neurocognitive performance in veterans. Results of the evaluation of Gulf War veterans suggested a statistically significant relationship between increased urinary uranium concentrations and poor performance on automated neuropsychologic tests regardless of the models used (24-hour-urine uranium in depleted-uranium–exposed veterans, $p = 0.01$; spot-urine uranium in all veterans, $p = 0.01$); traditional test measures showed no statistical differences between exposed and unexposed veterans (McDiarmid et al., 2000). However, the relationship between urinary uranium concentration and performance on automated measures observed in the 1994 and 1997 evaluations appeared to weaken and had only a marginal level of significance ($p = 0.098$) in high and low urinary-uranium groups in the 1999 surveillance after adjustment for intelligence (WRAT-3) and depression (Beck Depression Inventory) (McDiarmid et al., 2001). Later surveillance (2001, 2003, and 2005) found no statistically significant differences between exposure groups in neurocognitive indexes (McDiarmid et al., 2004; 2006; 2007). A modest association was seen between urinary uranium and the accuracy impairment (A-IIac) index in 2001 and 2003 surveillance, but the authors noted that the result was based on test performance of two veterans whose uranium concentrations were exceedingly high.

The committee concludes that there is inadequate/insufficient evidence to determine whether an association between exposure to uranium and nonmalignant diseases of the nervous system exists.

Overall, published studies of neurologic outcomes are either negative studies that do not find any evidence of health effects of exposure to depleted uranium or relatively small studies, such as the Depleted Uranium Follow-up Program at the BVAMC, that find inconstant associations. As described in Chapter 3, the results of studies in animal models indicate that depleted uranium is a toxicant capable of crossing the blood-brain barrier. Data on effects are inconsistent; some animal studies report behavioral changes, and others do not. Although at high concentrations different forms of uranium might be associated with some subtle neurologic dysfunction in animals, the relevance of these observations to humans remains unknown. On the

basis of the available evidence, the committee would assign a high priority to further study of an association between exposure to depleted uranium and neurologic effects.

Reproductive and Developmental Effects

A few studies examined the effects of natural or depleted uranium on human reproduction and development (see Table 8-18). McDiarmid and colleagues evaluated endocrinologic function in Gulf War veterans by measuring blood concentrations of follicle-stimulating hormone (FSH), luteinizing hormone (LH), prolactin, testosterone, thyroid-stimulating hormone, and free thyroxine. Study authors also assessed semen for a number of characteristics, including volume, concentration, structure, and motility. A statistically significant difference was observed in mean prolactin concentrations, which were 1.66 and 12.47 µg/g of creatinine ($p = 0.04$) in low- and high-prolactin groups (McDiarmid et al., 2000).

In the 1999 surveillance, there were no statistically significant differences in mean FSH, LH, prolactin, and testosterone concentrations or thyroid measures between low and high groups. Of the 44 sperm samples included in the analysis, three were designated subnormal—possessing below normal values of at least three of the five characteristics as defined by World Health Organization standards. The high-urinary-uranium groups had more abnormal total sperm counts (583.5 ± 106.1 vs 286.6 ± 44.8), total progressive sperm counts (220.9 ± 44.0 vs 108.2 ± 19.2), and total rapid progressive sperm counts (155.5 ± 31.1 vs 81.3 ± 15.4) that were statistically significant ($p = 0.02$, 0.03, and 0.04, respectively), results not previously seen in this group (McDiarmid et al., 2001). In 2001, overall neuroendocrine function was normal, but mean free thyroxine was higher in the low-uranium group (1.66 vs 1.08 ng/dL), a result not observed in the 1997 and 1999 evaluations. There was no statistically significant difference in semen measures between the high- and low-urinary-uranium groups (McDiarmid et al., 2004); this finding was consistent in successive evaluations. Increased mean values of semen characteristics were seen in the high-urinary-uranium group in the 2003 evaluation, but all were within the normal clinical ranges (McDiarmid et al., 2006). There were no statistically significant differences between high- and low-urinary-uranium groups in neuroendocrine measures, which were generally within normal clinical limits in veterans examined in the following surveillance. Mean values of semen characteristics also showed no statistically significant differences; however, the percentages of progressive sperm and rapid progressive sperm were lower in the high-uranium group on the basis of the current urinary-uranium metric (McDiarmid et al., 2007).

In a study of the prevalence of major malformations in two 1-year cohorts of neonates born in 1995 (immediately after the war in Bosnia) and in 2000 (5 years after military activities), 40 of 1,853 (2.16%) in 1995 had major malformations (95% CI, 1.49-2.82%), and 33 of 1,463 (2.26%) in 2000 had major malformations (95% CI, 1.50-3.01%). In addition, anomalies of the cardiovascular system (0.615% vs 0.162%) and central nervous system (0.273% vs 0%) were more elevated in the 2000 cohort than in the 1995 cohort (Sumanovic-Glamuzina et al., 2003).

The committee concludes that there is inadequate/insufficient evidence to determine whether an association between exposure to depleted uranium and reproductive and developmental effects exists.

Relatively large study populations are generally necessary to demonstrate significant but subtle reproductive or developmental effects. The studies reviewed generally had too few subjects or relied on insufficiently precise exposure assessment to support definitive conclusions.

Although some toxicology studies have reported that exposure of animals to uranium compounds during development can lead to a variety of adverse effects, others did not find that uranium exposure affected reproduction and development (see Chapter 3).

On the basis of the available evidence, the committee would assign a high priority to further study of an association between exposure to depleted uranium and reproductive and developmental effects.

Other Health Outcomes

The following discussion of additional health outcomes focuses on reported cardiovascular, hematologic, genotoxic, bone, and immunologic effects of exposure to natural or depleted uranium. The outcomes have not been studied in detail in humans, so the evidence from which to draw conclusions is sparse. The results presented here come primarily from a case series of Gulf War veterans who participated in the Depleted Uranium Follow-up Program at the BVAMC and from studies of uranium-processing workers and well-water users in Finland.

Cardiovascular Effects

Mortality from diseases of the circulatory system was significantly lower in most studies of uranium-processing workers, probably because of the healthy-worker effect. Pinkerton and colleagues reported statistically significantly fewer deaths from heart disease than expected (SMR, 84; 95% CI, 75-94) in a cohort of uranium-mill workers in the Colorado Plateau region (Pinkerton et al., 2004). Similarly, workers employed in the FFMPC had lower cardiovascular mortality than the US white male population (SMR, 78; 95% CI, 71-86) (Ritz, 1999). Mortality from circulatory diseases in workers at the Mallinckrodt processing plant (SMR, 89; 95% CI, 81-97) (Dupree-Ellis et al., 2000) and the Rocketdyne/Atomics International (SMR, 68; 95% CI, 58-78 (Ritz et al., 2000) was significantly lower than that in white males in the United States. Results of experimental studies that used exceedingly high doses of uranium in several animal models suggest that the cardiovascular system is not a sensitive target for this metal.

Genotoxic Effects[2]

McDiarmid and colleagues (2001) found a statistically significant increase in mean sister-chromatid exchanges (SCEs) (6.35 ± 0.267 vs 5.52 ± 0.182; $p = 0.03$) in cultured peripheral-blood lymphocytes from members of the high-urinary-uranium group in the 1999 medical surveillance of depleted-uranium–exposed Gulf War veterans. The association remained after adjustment for current smoking status. A statistically significant difference between low- and high-exposure groups was also seen in mean SCEs at high doses of bleomycin; the high-exposure group had increased SCEs (6.25 ± 0.338 vs 4.88 ± 0.262; $p = 0.01$). No differences were observed in tests for chromosomal aberrations. The findings suggest a possible genotoxic effect; however, as the authors suggest, additional surveillance was needed to establish a clinical association. In the 10-year postwar followup assessment, the authors reported a statistically significant increase in the mean frequency of chromosomal aberrations in the high-urinary-uranium group (McDiarmid et al., 2004). However, the 12- and 14-year assessments revealed no statistical differences in chromosomal aberrations between high- and low-urinary-uranium groups. Hypoxyanthine-guanine phosphoribosyl tranferase mutation frequencies measured at 10,

[2]Human genotoxic effects are covered in greater detail in Chapter 4.

12, and 14 years were nonsignificantly greater in the high-exposure group than in the low-exposure group.

Hematologic Effects

In general, hematologic measures in depleted-uranium–exposed Gulf War veterans were within normal clinical limits. Clinical tests revealed slight differences between high- and low-urinary-uranium groups. In a 1999 surveillance of veterans, hematologic measures exhibited statistically significant differences between high- and low-exposure groups. The high-urinary-uranium group had a lower mean lymphocyte count (32% vs 37%; $p = 0.04$), a higher mean neutrophil percentage (55% vs 49%; $p = 0.03$), and a lower mean monocyte percentage (7.6% vs 9.1%; $p = 0.01$) (McDiarmid et al., 2001). Differences in hematocrit (42.59% in the high-uranium group and 44.60% in the low-uranium group) and hemoglobin (14.79 vs 15.40 g/dL) that were not observed in the 1997 and 1999 surveillance were seen in 2001 (McDiarmid et al., 2004). The most recent evaluation found no statistically significant differences between high- and low-urinary-uranium groups in hematologic and blood-chemistry measures; they were within normal clinical limits (McDiarmid et al., 2007). Overall, increased urinary uranium excretion had little effect on hematologic measures.

Immunologic Effects

Only one study examined immunologic effects of depleted uranium. McDiarmid and colleagues found a significantly higher proportion of CD4+ T cells in the high- than in the low-uranium group (65.98% vs 60.83%), and CD8+ T cells were significantly lower in the high- than in the low-uranium group (26.55% vs 31.28%) (McDiarmid et al., 2004).

Skeletal Effects

In studies of the effect of uranium exposure on bone, researchers focused on biochemical markers of bone resorption and formation. In a study of Finnish well-water users, uranium exposure was shown to be associated with increased CTx (a bone-turnover marker) in men (uranium in water, $p = 0.05$ and 0.01; daily intake, $p = 0.16$ and 0.02; and cumulative intake, $p = 0.16$ and 0.03, in the robust and linear-regression analyses, respectively). In addition, uranium concentrations in drinking water appeared to be associated with increased osteocalcin, a biomarker often used for bone formation ($p = 0.19$; $p = 0.04$ in linear-regression analysis). Uranium exposure was not related to any biomarkers of bone metabolism in women. Amino-terminal propeptide of type I procollagen was not associated with uranium exposure (Kurttio et al., 2005). In an analysis of tissue collected during an autopsy of a uranium-processing worker, uranium was found to be deposited more in bone than in the liver or kidneys (Kathren et al., 1989).

Conclusion

The committee concludes that there is inadequate/insufficient evidence to determine whether an association between exposure to uranium and cardiovascular, genotoxic, hemotologic, immunologic, and skeletal effects exists.

SUMMARY

This chapter summarized the committee's systematic evaluation of the scientific literature about the human health outcomes of exposure to uranium. Overall, the committee concluded that the available data are inadequate and insufficient to support statements that exposure to uranium is associated with the health outcomes or statements that exposure to uranium is *not* associated with the health outcomes. The inability to reach positive or negative conclusions is due largely to limitations of the available scientific literature. Studies that permit more definitive conclusions might become available in the future.

The committee's review and evaluation of the scientific literature placed particular emphasis on epidemiologic studies. Toxicologic data were considered secondary and were used largely to determine mechanism of action. The committee used direct evidence (that is, from the empirical literature) rather than relying on a theory-driven approach (that is, using mechanistic models) in drawing its conclusions.

Most of the evidence on health outcomes of exposure to uranium comes from studies of workers in uranium-processing mills and other facilities, and the committee relied heavily on those studies in developing its conclusions. It also considered studies of Gulf War veterans who were exposed to depleted uranium and studies of residential exposure to uranium. The committee selected studies that it believed to be the most relevant to identifying health outcomes in depleted-uranium–exposed military personnel. Although numerous epidemiologic studies of various forms of radiation exposure have been conducted, the committee limited its review to studies of exposure to uranium (both natural and depleted uranium).

The use of the epidemiologic literature in developing conclusions presented several limitations. For example, the number of exposed people in many of the studies was relatively small, and this decreased the statistical power to detect small excesses of disease. The period of followup in several studies might have been too short to detect some diseases that are typically characterized by long latency; this limitation is of particular concern in regard to studies of cancer outcomes. Appropriate classification of study subjects according to exposure status also constituted a limitation. Inaccurate or imprecise characterization of the exposure of each person in a study may reduce the likelihood of detecting a health outcome associated with exposure or, conversely, could lead to the appearance of an association when none exists. Assessment of exposure to uranium was inadequate in many of the studies reviewed by the committee.

The likelihood of detecting an association between exposure and a health outcome depends on several factors (see Chapter 4). For the health outcomes discussed in this chapter, the committee concluded that exposure to uranium is not associated with a large or frequent effect. Nevertheless, it is possible that depleted-uranium–exposed veterans will have a small increase in the likelihood of developing a disease. Typically, extremely large study populations are necessary to demonstrate that a specific exposure is not associated with a health outcome. The committee's evaluation of the literature supports the conclusion that a large or frequent effect is unlikely, but it is not possible to state conclusively that a particular health outcome can not occur.

In summary, the committee assigned the category *inadequate/insufficient evidence to determine whether an association exists* to each health outcome described above for one or more of the following reasons:

- Well-conducted studies showed equivocal results.
- The magnitude or frequency of a health outcome may be so low that it cannot be reliably detected given the sizes of the study populations.
- The available studies had limitations (for example, inadequate exposure assessment or followup that was too short) that prevented the committee from reaching clear conclusions about health outcomes.

For those reasons, a conclusion of inadequate/insufficient evidence to determine whether an association exists is not synonymous with evidence of no association.