The 1991 Persian Gulf War was considered a brief and successful military operation with few injuries and deaths. The returning veterans, however, soon began reporting numerous health problems that they believed to be associated with their service in the gulf. Many Gulf War veterans returned to normal activities, but a large number have had a wide array of unexplained illnesses.

In response to the growing concerns of ill Gulf War veterans, Congress passed two laws in 1998: PL 105-277, the Persian Gulf War Veterans Act, and PL 105-368, the Veterans Programs Enhancement Act. Those laws directed the secretary of veterans affairs to enter into a contract with the National Academy of Sciences (NAS) to review and evaluate the scientific and medical literature regarding associations between illness and exposure to toxic agents, to environmental or wartime hazards, or to preventive medicines or vaccines associated with Gulf War service and to consider the NAS conclusions when making decisions about compensation. The study was assigned to the Institute of Medicine (IOM).

The Persian Gulf War legislation directs IOM to study a wide array of biologic, chemical, and physical agents. Given the large number of agents to study, IOM divided the task into several reviews. It has completed two reviews – *Gulf War and Health, Volume 1: Depleted Uranium, Pyridostigmine Bromide, Sarin, and Vaccines* and *Gulf War and Health, Volume 2: Insecticides and Solvents* – and has recently conducted an update of the sarin review in *Gulf War and Health: Updated Literature Review of Sarin.* The current volume examines the health effects of hydrazines, red fuming nitric acid, hydrogen sulfide, oil-fire byproducts, diesel-heater fumes, and fuels (for example, jet fuel and gasoline).

CHARGE TO THE COMMITTEE

In accordance with PL 105-368 and PL 105-277, IOM appointed the Committee on Gulf War and Health, Literature Review of Selected Environmental Particulates, Pollutants, and Synthetic Chemical Compounds and asked it to determine the following to the extent that available scientific data permit meaningful conclusions:

(A) whether a statistical association exists between exposure to the agent, hazard, or medicine or vaccine and the illness, taking into account the strength of the scientific evidence and the appropriateness of the scientific methods used to detect the association,

- (B) the increased risk of the illness among human or animal populations exposed to the agent, hazard, or medicine or vaccine,
- (C) whether a plausible biologic mechanism or other evidence of a causal relationship exists between exposure to the agent, hazard, or medicine or vaccine and the illness.

It should be noted that the charge to IOM was not to determine whether a unique Gulf War syndrome exists or to make judgments about whether veterans were exposed to the putative agents. Nor was the charge to focus on broader issues, such as the potential costs of compensation for veterans or policy regarding compensation; such decisions are the responsibility of the secretary of veterans affairs.

Evidence of Statistical Association

The committee reviewed the available scientific evidence in the peer-reviewed literature to draw conclusions about associations between the agents of interest and adverse health effects. The committee placed its conclusions in categories that reflect the strength of the evidence of an association (described below). In an effort to determine whether a statistical association between a putative agent and a health outcome exists, the committee adapted categories of association used by the International Agency for Research on Cancer in evaluating evidence of the carcinogenicity of various agents and categories used by numerous other IOM committees.

Determining Increased Risk in Gulf War Veterans

The second part of the committee's charge is to determine, to the extent permitted by available scientific data, the increased risk of illness among people exposed to the putative agents during service in the Persian Gulf. Generally, to accomplish that task, the committee would have reviewed studies of Gulf War veterans. However, many of the Gulf War veteran studies were hampered by poor measures of exposure to the putative agents, used questionnaires to identify illnesses and exposure to the agents of concern, or did not include outcomes measured with clinical examinations or laboratory tests. The committee therefore based its conclusions primarily on evidence from studies of people exposed to the putative agents in occupational or clinical settings rather than evidence from studies of Persian Gulf veterans. The committee found the evidence from occupational studies adequate for drawing conclusions about associations between the putative agents and health outcomes, but the lack of adequate data on the veterans themselves complicated its consideration of the second part of the charge: determination of increased risk in Gulf War veterans.

To estimate the magnitude of risk of a particular health outcome among Gulf War veterans, the committee would need to compare the rates of disease or other health effects in veterans exposed to the putative agents with the rates in those who were not exposed. That would require information about the specific agents to which individual veterans were exposed and

about their doses. However, there is a paucity of data regarding the agents and doses to which individual Gulf War veterans were exposed. Furthermore, to answer questions about increased risk of illnesses in Gulf War veterans, it would be important to know the degree to which any other differences between exposed and nonexposed veterans could influence the rates of disease or other health outcomes; such information on the Gulf War veteran population is lacking. Because of the lack of various kinds of data on veterans, the committee could not extrapolate from the exposures in the studies that it reviewed to the exposures of Gulf War veterans. Therefore, it could not determine the likelihood of increased risk of adverse health outcomes among Gulf War veterans due to exposure to the agents examined in this report.

Existence of a Plausible Biologic Mechanism or Other Evidence of a Causal Relationship

Toxicologic data form the basis of the committee's response to the third part of its charge: to determine whether there is a plausible biologic mechanism or other evidence of a causal relationship between exposure to a particular agent and a health effect. Although toxicologic studies played a small role in determining the likelihood that an exposure to a specific agent might cause a long-term health outcome, the committee used evidence from toxicologic studies to assess biologic plausibility in support of epidemiologic data.

COMMITTEE'S APPROACH TO ITS CHARGE

Identification and Evaluation of the Literature

The committee began its evaluation by presuming neither the existence nor the absence of associations. It has sought to characterize and weigh the strengths and limitations of the available evidence. The committee's task was not to judge individual cases of particular diseases or conditions or to address questions of causation. Nor did the committee concern itself with policy issues, such as potential costs of compensation, policy regarding compensation, or any broader policy implications of its findings.

Extensive searches of the epidemiologic literature were conducted on the agents identified for study, and over 33,000 potentially relevant references were retrieved. After an assessment of the titles and abstracts of the initial searches, the committee focused on some 800 potentially relevant epidemiologic studies for review and evaluation.

Because only a few studies were related directly to veterans' exposures, the committee reviewed primarily occupational studies of populations that had been exposed to the agents of interest. Those studies often included people whose exposures had been over a lifetime (such as to air pollution in their communities) or included workers employed in a particular industry over many years. In contrast, the exposures of veterans in the Persian Gulf were of relatively short duration with varying intensity. Therefore, the exposures experienced during the Gulf War might only approximate the exposures described in the occupational and environmental literature reviewed in this report. The conclusions of statistical associations based on occupational studies are meant to serve as a guide to potential health effects associated with specific agents.

The committee adopted a policy of using only peer-reviewed published literature as the basis of its conclusions. Publications that were not peer-reviewed had no evidentiary value for the committee; that is, they were not used as evidence for arriving at conclusions about the degree of association between exposure to a particular agent and adverse health effects. The process of peer review by fellow professionals ensures high standards of quality but does not guarantee the validity of a study or the ability to generalize its results. Accordingly, committee members read each study critically and considered its relevance and quality. The committee did not collect original data, nor did it perform any secondary data analysis.

It should be noted that our available scientific tools—toxicology and epidemiology—are inadequate to illuminate clearly the human health effects of individual components of complex mixtures of the type experienced by Gulf War veterans. In many cases, the committee found "inadequate/insufficient evidence of an association" between the exposure of concern and a health outcome; that may have been due to a lack of clear evidence because of the inadequacy of those tools rather than to the absence of effects.

Inclusion Criteria

The committee's next step, after securing the full text of some 800 epidemiologic studies, was to determine which studies would be included in the review as primary or support studies. Therefore, the committee developed inclusion criteria. For a study to be included in the committee's review it had to meet specified criteria, for example, methodologic rigor, identification of class or agent, specificity of health outcome, an exposure assessment, and in some cases, an exposure-free interval. For relevance to the Gulf War veterans, the committee focused on long-term health outcomes that persist after exposure ceases.

Considerations in Assessing the Strength of the Evidence

The committee's process of reaching conclusions about the various agents and their potential for adverse health outcomes was collective and interactive. Once a study was included in the review because it met the committee's criteria, there were several considerations in assessing the strength of an association. They are patterned after those introduced by Hill in 1971 and include strength of the evidence for an association, dose-response relationship, temporal relationship, consistency of association specificity of association, and biologic plausibility. The committee also considered whether alternative explanations or errors—such as, bias, confounding, and chance—might account for the finding of an association.

The committee's final judgment, therefore, is based on a balance between the strength of support of an association and the degree of exclusion of alternatives. The evaluation of evidence to reach conclusions about statistical associations goes beyond quantitative procedures; several stages during the review required thoughtful consideration and judgment and could not always be accomplished by adherence to a prescribed formula.

The approach described here evolved throughout the process of review and was determined in important respects by the nature of the evidence, exposures, and health outcomes being examined. Both quantitative and qualitative aspects of the process were important to the

overall review. Ultimately, the conclusions expressed in this report are based on the committee's collective judgment.

CATEGORIES OF ASSOCIATION

The committee classified the evidence of an association between exposure to a specific agent and a specific health outcome into five categories. The categories have been developed by previous IOM committees and have been used to evaluate vaccine safety, herbicides used in Vietnam, and indoor pollutants related to asthma.

Sufficient Evidence of a Causal Association

Evidence is sufficient to conclude that there is a causal association between exposure to a specific agent and a specific health outcome in humans. The evidence is supported by experimental data and fulfills the guidelines for sufficient evidence of an association (below). The evidence must be biologically plausible and satisfy several of the guidelines used to assess causality, such as strength of association, dose-response relationship, consistency of association, and temporal relationship.

Sufficient Evidence of an Association

Evidence is sufficient to conclude that there is an association. That is, a consistent association has been observed between exposure to a specific agent and a specific health outcome in human studies in which chance¹ and bias, including confounding, could be ruled out with reasonable confidence. For example, several high-quality studies report consistent associations, and the studies are sufficiently free of bias, including adequate control for confounding.

Limited/Suggestive Evidence of an Association

Evidence is suggestive of an association between exposure to a specific agent and a specific health outcome, but the body of evidence is limited by the inability to rule out chance and bias, including confounding, with confidence. For example, at least one high-quality² study reports an association that is sufficiently free of bias, including adequate control for confounding, and other corroborating studies provide support for the association but are not

¹Chance refers to sampling variability.

²Factors used to characterize high-quality studies include the statistical stability of the association, whether a doseresponse or other trend was demonstrated, whether the association was among numerous comparisons that were made, and the quality of the assessments of exposure and outcome. Specifically, the quality of exposure assessment refers to specificity and sensitivity in relation to the association of interest. Biologic monitoring data, such as markers of exposure, are theoretically the most preferable but are almost never obtainable in the context of a nonpersistent chemical. Other kinds of efforts can obtain sensitive measures of exposure, such as use of interview techniques that minimize recall bias, an assessment of occupational history by a panel of experts, and estimating exposure intensity independent of health outcome.

sufficiently free of bias, including confounding. Alternatively, several studies of lower quality show consistent associations, and the results are probably not³ due to bias, including confounding.

Inadequate/Insufficient Evidence To Determine Whether an Association Exists

Evidence is of insufficient quantity, quality, or consistency to permit a conclusion regarding the existence of an association between exposure to a specific agent and a specific health outcome in humans.

Limited/Suggestive Evidence of No Association

Evidence is consistent in not showing an association between exposure to a specific agent and a specific health outcome after exposure of any magnitude. A conclusion of no association is inevitably limited to the conditions, magnitudes of exposure, and length of observation in the available studies. The possibility of a very small increase in risk after exposure cannot be excluded.

The committee endeavored to express its judgment as clearly and precisely as the available data allowed, and it used the established categories of association from previous IOM studies because they have gained wide acceptance over more than a decade by Congress, government agencies, researchers, and veterans groups. The five categories describe different degrees of association and sound a recurring theme: the validity of an association is likely to vary with the extent to which the authors reduced common sources of error—chance variation, bias, and confounding—in drawing inferences. Accordingly, the criteria for each category express a degree of confidence based on the extent to which sources of error were reduced.

HUMAN HEALTH OUTCOMES

The committee reviewed numerous epidemiologic studies to arrive at conclusions about association. The committee weighed the strengths and limitations of all the epidemiologic studies and reached its conclusions by interpreting the data in the entire body of reviewed literature. It assigned each health outcome being considered to one of the five categories of association according to the criteria set forth above. The health outcomes that were indicated by the epidemiologic studies were numerous and include cancer, respiratory, cardiovascular, reproductive, and neurologic outcomes. In many cases, the health outcomes described might also result from genetics or lifestyle factors; for example, according to the American Cancer Society, smoking is believed to be responsible for about 80% of lung-cancer cases.

The committee's findings about the strength of the associations between the putative agents and the health outcomes are summarized in Table ES-1.

³Factors used to make this judgment include the data on the relationship between potential confounders and related health end points in a given study, information on subject selection, and classification of exposure.

SUMMARY OF FINDINGS

Although Table ES-1 provides a summary of all the committee's conclusions, the committee wishes to note that the starting point for any health outcome before study is, of course, the category of inadequate or insufficient evidence of an association. Of all the health outcomes on which any evidence was culled from the epidemiologic literature, none was found to be associated in even a limited or suggestive fashion with the uncombusted fuels that veterans may have been exposed to during the Gulf War (with the exception of benzene, a component of fuels, which was reviewed by a previous IOM committee and not reassessed in this report).

The strongest finding was that there is sufficient evidence of an association between combustion products and lung cancer. The committee also found limited or suggestive evidence of an association between combustion-product exposure and cancers at several other sites (oral, nasal, laryngeal, and bladder), incident asthma, and two reproductive outcomes after exposure during pregnancy: preterm birth and low birthweight or intrauterine growth retardation. For the propellant components of Scuds, only hydrazines were found to have a suggestive association with lung cancer.

Finally, it should be repeated that the committee was charged with reviewing the scientific data, not with making recommendations regarding the Department of Veterans Affairs policy; therefore, conclusions are not intended to imply or suggest policy decisions. Furthermore, the conclusions are related to associations between exposure to the agents under study and health outcomes in human populations, not to the likelihood that any one person's health problem is associated with or caused by exposure to the agents.

TABLE ES.1 Summary of Findings Regarding the Association Between Exposure to Fuels, Combustion Products, Hydrazines, and Nitric Acid and Specific Health Outcomes

Sufficient Evidence of a Causal Relationship

Evidence is sufficient to conclude that there is a causal association between exposure to a specific agent and a specific health outcome in humans. The evidence is supported by experimental data and fulfills the guidelines for sufficient evidence of an association (below). The evidence must be biologically plausible and satisfy several of the guidelines used to assess causality, such as: strength of association, dose—response relationship, consistency of association, and a temporal relationship.

No conclusions

Sufficient Evidence of an Association

Evidence is sufficient to conclude that there is a positive association. That is, a consistent positive association has been observed between exposure to a specific agent and a specific health outcome in human studies in which chance and bias, including confounding, could be ruled out with reasonable confidence. For example, several high-quality studies report consistent positive associations, and the studies are sufficiently free of bias, including adequate control for confounding.

• Combustion products and lung cancer

Limited/Suggestive Evidence of an Association

Evidence is suggestive of an association between exposure to a specific agent and a specific health outcome, but the body of evidence is limited by the inability to rule out chance and bias, including confounding, with confidence. For example, at least one high-quality study reports a positive association that is sufficiently free of bias, including adequate control for confounding. Other corroborating studies provide support for the association, but they were not sufficiently free of bias, including confounding. Alternatively, several studies of lower quality show consistent positive associations, and the results are probably not due to bias, including confounding.

Cancers

- Combustion products and
 - o Cancers of the nasal cavity and nasopharynx
 - Cancers of the oral cavity and oropharynx
 - o Laryngeal cancer
 - o Bladder cancer
- Hydrazines and lung cancer

Reproductive Effects

- Combustion products and
 - Low birthweight/intrauterine growth retardation and exposure during pregnancy
 - o Preterm birth and exposure during pregnancy

Respiratory Effects

Combustion products and incident asthma

Inadequate/Insufficient Evidence

Evidence is of insufficient quantity, quality, or consistency to permit a conclusion regarding the existence of an association between exposure to a specific agent and a specific health outcome in humans.

Cancers

- Fuels and
 - Cancers of the oral cavity and oropharynx
 - o Cancers of the nasal cavity and nasopharynx
 - Esophageal cancer
 - Stomach cancer
 - Colon cancer
 - Rectal cancer
 - Hepatic cancer
 - o Pancreatic cancer
 - o Laryngeal cancer
 - o Lung cancer
 - o Melanoma
 - o Nonmelanoma skin cancer
 - Female breast cancer
 - Male breast cancer

- o Female genital cancers (cervical, endometrial, uterine, and ovarian cancers)
- o Prostatic cancer
- Testicular cancer
- o Nervous system cancers
- Kidney cancer
- o Bladder cancer
- o Hodgkin's disease
- o Non-Hodgkin's lymphoma
- o Multiple myeloma
- o Myelodysplastic syndromes

• Combustion products and

- o Esophageal cancer
- o Stomach cancer
- Colon cancer
- o Rectal cancer
- o Hepatic cancer
- o Pancreatic cancer
- o Melanoma
- o Female breast cancer
- o Male breast cancer
- o Female genital cancers (cervical, endometrial, uterine, and ovarian cancers)
- o Prostatic cancer
- o Testicular cancer
- o Nervous system cancers
- o Ocular melanoma
- Kidney cancer
- o Non-Hodgkin's lymphoma
- o Hodgkin's disease
- o Multiple myeloma
- o Leukemia
- o Myelodysplastic syndromes

Hydrazines and

- Hematopoietic and lymphopoietic cancers
- o Digestive tract cancers
- o Pancreatic cancer
- o Bladder cancer
- Kidney cancer

• Nitric acid and:

- Stomach cancer
- o Melanoma
- Lymphopoietic cancers
- o Pancreatic cancer
- o Laryngeal cancer
- Lung cancer
- Bladder cancer

o Multiple myeloma

Reproductive Effects

- Fuels and adverse reproductive or developmental outcomes (including infertility, spontaneous abortion, childhood leukemia, CNS tumors, neuroblastoma, and Prader-Willi syndrome)
- Combustion products and
 - o Preterm births and exposure during any specific time period during pregnancy (for example, the first trimester)
 - Low birth weight and intrauterine growth retardation and exposure before gestation or during any specific period during pregnancy (for example, the first trimester)
 - o Specific birth defects, including cardiac effects, and exposure before conception (maternal and paternal) or during early pregnancy (maternal)
 - o All childhood cancers identified, including acute lymphocytic leukemia, leukemia, neuroblastoma, and brain cancer

Neurologic Effects

- Fuels and
 - o Peripheral neuropathy
 - o Neurobehavioral effects
 - o Multiple Chemical Sensitivity symptoms
- Combustion products and
 - Neurobehavioral effects
 - o Posttraumatic stress disorder
 - o Nervous system subgroupings (or individual nervous system diseases)
 - o Multiple Chemical Sensitivity symptoms

Respiratory Effects

- Fuels and
 - o Nonmalignant respiratory disease
 - o Chronic bronchitis
 - o Asthma
 - o Emphysema
- Combustion products and:
 - o Chronic bronchitis (less than 1 year of exposure)
 - o Emphysema
 - o Chronic obstructive pulmonary disease
- Hydrazines and emphysema

Cardiovascular Effects:

- Combustion products and ischemic heart disease or myocardial infarction (less than 2 years of exposure)
- Hydrazines and ischemic heart disease or myocardial infarction
- Nitric acid and cardiovascular diseases

Dermal Effects:

- Fuels and dermatitis—irritant and allergic
- Combustion products and dermatitis—irritant and allergic

Other Health Effects:

- Fuels and sarcoidosis
- Combustion products and sarcoidosis
- Hydrazines and hepatic disease

Limited/Suggestive Evidence of No Association

Evidence is consistent in not showing a positive association between exposure to a specific agent and a specific health outcome after exposure of any magnitude. A conclusion of no association is inevitably limited to the conditions, magnitudes of exposure, and length of observation in the available studies. The possibility of a very small increase in risk after exposure studied cannot be excluded.

• No conclusions