EXECUTIVE SUMMARY

The Gulf War was considered a brief and successful military operation, with few injuries and deaths of US troops. The war began in August 1990, and the last US ground troops returned home by June 1991. Although most Gulf War veterans resumed their normal activities, many began reporting a variety of unexplained health problems that they attributed to their participation in the Gulf War, including chronic fatigue, muscle and joint pain, loss of concentration, forgetfulness, headache, and rash.

One response to concerns about the veterans' health problems was a request by the Department of Veterans Affairs (VA) that the Institute of Medicine (IOM) review the scientific and medical literature on the long-term adverse health effects of biologic and chemical agents to which the Gulf War veterans may have been exposed. In 1998, IOM and VA entered into a contract for a series of studies that would provide conclusions about the strength of associations between exposure to the agents of concern and health outcomes as observed in the epidemiologic literature.

Congress, also responding to the growing concerns of ill veterans, passed legislation in 1998 (the Persian Gulf War Veterans Act, PL 105-277, and the Veterans Programs Enhancement Act, PL 105-368) for a study similar to that previously requested by VA. The legislation directed the secretary of veterans affairs to enter into an agreement with IOM to review the literature on 33 biologic and chemical agents and groups of agents believed to be associated with service in the Gulf War and to assess the strength of the evidence of associations between exposure to the agents and long-term adverse health effects. The legislation directed the secretary to consider the IOM conclusions when making decisions about compensation.

The following agents are listed in PL 105–277 and PL 105–368:

Pesticides: organophosphorus pesticides (chlorpyrifos, diazinon, dichlorvos, and malathion), carbamate pesticides (proxpur[1], carbaryl, and methomyl), and chlorinated-hydrocarbons and other pesticides and repellents (lindane, pyrethrins, permethrins[2], rodenticides [bait], and the repellent DEET [*N,N*-diethyl-3-methylbenzamide])

Pyridostigmine bromide

[1] The committee searched and examined the literature on the insecticide propoxur.
[2] Permethrin is the name of a specific pyrethroid insecticide.

Nerve agents and precursor compounds: sarin and tabun

Synthetic chemical compounds: mustard agents, volatile organic compounds, hydrazine, red fuming nitric acid, and solvents

Environmental particles and pollutants: hydrogen sulfide, oil-fire byproducts, diesel heater fumes, and sand microparticles

Sources of radiation: uranium, depleted uranium, microwave radiation, and radiofrequency radiation

Diseases endemic to the region: leishmaniasis, sandfly fever, pathogenic *Escherichia coli*, and shigellosis

Administration of live, "attenuated", and toxoid vaccines.

In response to VA and Congress, IOM determined that the study would be conducted in phases and that the initial phase would include a review of the agents that were of most concern to the veterans. After meetings with Gulf War veterans, the first IOM Gulf War committee decided that its study would focus on depleted uranium, pyridostigmine bromide, sarin, and vaccines (anthrax and botulinum toxoid).

After reviewing IOM's *Gulf War and Health, Volume I,* the secretary of veterans affairs determined that there was no basis to establish a presumption of a connection between Gulf War exposure to sarin, pyridostigmine bromide, depleted uranium, or anthrax or botulinum toxoid vaccine and various health outcomes.

SCOPE OF VOLUME 2

This second volume focuses on long-term adverse health outcomes associated with exposure to insecticides and solvents. The IOM committee that was formed to conduct the second study began its work by overseeing extensive searches of the peer-reviewed medical and scientific literature. The searches retrieved about 30,000 potentially relevant references which were considered by the committee and staff. After an assessment of the references, the committee focused on about 3000 that analyzed the relevant insecticides and solvents and their long-term adverse health effects in humans. The committee did not review the literature on short-term outcomes, inasmuch as the veterans, their families, VA, and Congress are concerned with health effects that might persist long after exposure ceased and that might require compensation.

It should be noted that the charge to IOM was not to determine whether a unique Gulf War syndrome exists or to judge 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 such compensation; that policy is the responsibility of the secretary of veterans affairs. The committee's charge was to assess the scientific evidence regarding long-term health effects associated with exposure to specific agents that were potentially present during the Gulf War. Epidemiologic studies that analyzed the relationship between exposure to specific chemicals under review and long-term health outcomes provided the evidence for the committee to use in drawing conclusions of association.

METHODS

As the committee began its task, the first step was to broadly identify the literature for review. Searches were conducted by using the names and synonyms of the specific insecticides and solvents identified for study, their Chemical Abstract Registry numbers, and the relevant classes of insecticides and solvents. Searches were also conducted on occupations with known exposure to insecticides or solvents (such as pesticide application, painting, and dry cleaning). Finally, background documents and reviews of experimental evidence were retrieved and examined.

The literature search resulted in the retrieval of about 30,000 titles. As the titles and abstracts were reviewed, it became apparent that many of the studies were not relevant to the committee's task. The committee therefore developed inclusion criteria for the studies to be reviewed; for example, there had to be an examination of the agents under consideration, the study design had to be appropriate for the committee's task of weighing evidence, and the study had to be an original study rather than a review or meta-analysis. Results of the studies also had to demonstrate persistent rather than short-term effects. Applying those criteria helped the committee to narrow the 30,000 titles and abstracts to about 3000 peer-reviewed studies that would be carefully reviewed. The studies were primarily occupational-studies, of workers exposed chronically to insecticides or solvents, including studies of Gulf War veterans that specifically examined insecticide and solvent exposure. Examples of studies excluded from review were those which focused solely on the efficacy of insecticide use in mitigating the effects of insect infestation or examined pesticide ingestion and suicide. Similarly, studies of occupations with exposure to multiple agents and those without specificity of agent (for example, farming and agricultural work) were excluded in that it was difficult to determine the agent responsible for an outcome. Case studies of acute poisonings or short-term outcomes were also excluded.

It should be noted that animal studies had a limited role in the committee's assessment of association between exposure and health outcome. Animal data were used for making assessments of biologic plausibility; they were not used as part of the weight-of-evidence approach to determining likelihood that an exposure to a specific agent might have a specific long-term outcome. The animal studies were, however, used as evidence to support the epidemiologic data.

The committee did not collect original data or perform secondary data analysis. It did, however, calculate confidence intervals, when a study did not provide them, on the basis of the number of subjects (cases and controls), the relative risk or odds ratio, or the p value.

DRAWING CONCLUSIONS ABOUT THE LITERATURE

As noted, the committee adopted a policy of using only published, peer-reviewed literature to draw its conclusions. Although the process of peer review by fellow professionals enhances the likelihood that a study has reached valid conclusions, it does not guarantee validity. Accordingly, committee members read each study and considered its relevance and quality.

The committee classified the evidence of association between exposure to a specific agent and a specific health outcome into five previously established categories, as set forth below. The categories closely resemble those used by several IOM committees that have evaluated vaccine safety, herbicides used in Vietnam, and indoor pollutants related to asthma. The first three categories imply a statistical association, the committee's conclusions are based on the strength and coherence of the findings in the available studies. The conclusions represent the committee's collective judgment. The committee endeavored to express its judgment as clearly and precisely as the available data allowed. 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.

However, inasmuch as each committee member relied on his or her training, expertise, and judgment, the committee's conclusions have both quantitative and qualitative aspects. In some cases, committee members were unable to agree on the strength of evidence of an association under review; in such instances, if a consensus conclusion could not be reached, the committee presents their different points of view in the text.

The five categories describe different levels 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 in making inferences—chance variation, bias, and confounding. Accordingly, the criteria for each category express a degree of confidence based on the extent to which sources of error were reduced. The five categories and their rationale are as follows.

Sufficient Evidence of a Causal Relationship

Evidence from available studies is sufficient to conclude that a causal relationship exists between exposure to a specific agent and a specific health outcome in humans, and the evidence is supported by experimental data. The evidence fulfills the guidelines for sufficient evidence of an association (below) and satisfies several of the guidelines used to assess causality: strength of association, dose–response relationship, consistency of association, and a temporal relationship.

Sufficient Evidence of an Association

Evidence from available studies is sufficient to conclude that there is a positive association. A consistent positive association has been observed between exposure to a specific agent and a specific health outcome in human studies in which chance[3] 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.

Limited/Suggestive Evidence of an Association

Evidence from available studies suggests an association between exposure to a specific agent and a specific health outcome in human studies, but the body of evidence is limited by the inability to rule out chance and bias, including confounding, with confidence. For

[3]Chance refers to sampling variability.

example, at least one high-quality[4] 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 less quality show consistent positive associations, and the results are probably not[5] due to bias, including confounding.

Inadequate/Insufficient Evidence to Determine Whether an Association Exists

Evidence from available studies 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 from available studies 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.

As the committee began its evaluation, neither the existence nor the absence of an association was presumed. Rather, the committee weighed the strengths and weaknesses of the available evidence to reach conclusions in a common format. It should be noted that although causation and association are often used synonymously, the committee distinguishes between "sufficient evidence of a causal relationship" and "sufficient evidence of an association". An association can indicate an increase in risk without the agent(s) being the sole or even primary cause.

Epidemiologic studies can establish statistical associations between exposure to specific agents and specific health effects, and associations are generally estimated by using relative risks or odds ratios. To conclude that an association exists, it is necessary for an agent to occur with the health outcome more frequently than expected by chance and it is almost always necessary to find that the effect occurs consistently in several studies. Epidemiologists seldom consider one study taken alone as sufficient to establish an association; rather, it is desirable to replicate the findings in other studies for conclusions to

[4]Factors used to characterize high quality studies include, the statistical stability of the associations, whether a dose– response or other trends were 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. For instance, for insecticides, studies assessing specific insecticides (such as chlorpyrifos) have more specificity than those assessing classes of insecticides (such as organophosphorous) which in turn are more specific than those assessing pesticides more generally. With respect to sensitivity, studies are judged by the instruments used to measure exposure. Biologic monitoring data are theoretically the most preferable but are almost never obtainable in the context of a nonpersistent chemical and a disease with long latency, like cancer. Other kinds of efforts can obtain sensitive measures of exposure, such as use of occupational or environmental monitoring data, use of more extensive industrial hygiene assessments, use of interview techniques that help to minimize recall bias (for example, photos of products, and home and workplace walkthroughs). Similarly, there are questions about quality of outcome assessment–whether an outcome has been verified by a medical diagnosis in a consistent fashion.

[5]Factors 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.

be drawn about the association. Results from separate studies are sometimes conflicting. It is sometimes possible to attribute discordant study results to such characteristics as the soundness of study design, the quality of execution, and the influence of different forms of bias. Studies that result in a statistically significant measure of association account for the role of chance in producing the observed result. When the measure of association does not show a statistically significant effect, it is important to consider the size of the sample and whether the study had the power to detect an effect if it existed.

Study designs differ in their ability to provide valid estimates of an association. Randomized controlled trials yield the most robust type of evidence, whereas cohort or case–control studies are more susceptible to bias. Cross–sectional studies, in general, provide a lower level of evidence than cohort and case–control studies. Determining whether a given statistical association rises to the level of causation requires inference. To assess explanations other than causality, one must bring together evidence from different studies and apply well-established criteria that have been refined over more than a century. Thus, by examining numerous epidemiologic studies, the committee addresses the question, "Does the available evidence support a causal relationship or an association between a particular exposure and a specific health outcome?" An association between a specific agent and a specific health outcome does not mean that exposure to the agent invariably results in the health outcome or that all cases of the health outcome are the result of exposure to the agent. Such complete correspondence between exposure and disease is the exception in the study of disease in large populations. The committee evaluated the data and based its conclusions on the strength and coherence of the data in the selected studies. The committee's final conclusions represent its collective judgment; each committee member presented and discussed conclusions with the entire committee. In some cases committee members strongly believed that the literature supported, for example, a conclusion of "limited/suggested evidence of an association" when other members, on examination of the data, might have concluded that the evidence was "inadequate/insufficient of an association." In those instances, if a consensus conclusion could not be reached, opposing points of view are presented, and the committee notes that further research is needed to resolve the uncertainty.

Although the committee focused primarily on epidemiologic studies when drawing conclusions, there is a limited role for experimental evidence. Many of the chemicals that are examined in this report have been extensively studied in animals. A complete summary of all the available data on all the solvents and insecticides under review would fill many volumes. Given the small role of experimental studies in this report in the categorization of evidence, such a detailed review would serve no purpose. Instead, the report provides only a broad picture of the most important experimental toxicity data available in reliable secondary sources. For conclusions of "sufficient evidence of a causal relationship", the relevant experimental data are discussed where such a characterization is supported.

CONCLUSIONS

The following is a summary of the committee's conclusions on health outcomes associated with exposure to specific insecticides and solvents. If the entire committee did not agree on a conclusion, then the association was not assigned a category. It so happens

that in each instance (listed below), the committee could not reach consensus on whether the association was limited/suggestive or inadequate/insufficient. The issues associated with the non-consensus associations are discussed in the text.

Consensus Not Reached on Category of Association

- Tetrachloroethylene and dry-cleaning solvents and esophageal cancer
- Trichloroethylene and colon cancer
- Mixtures of benzene, toluene, and xylene and colon cancer
- Tetrachloroethylene and dry-cleaning solvents and lung cancer
- Trichloroethylene and cervical cancer
- Solvents and kidney cancer.
- Benzene and solvents and brain and other central nervous system cancers
- Parental preconception exposure to solvents and childhood leukemia
- Organophosphorus insecticide exposure without OP poisoning and long-term neurobehavioral effects (that is, abnormal results on neurobehavioral test batteries and symptom findings)

Summary of the Committee's Consensus Conclusions

(NB: these conclusions pertain to the particular insecticides and solvents identified as having been shipped to the Persian Gulf.)

SUFFICIENT EVIDENCE OF A CAUSAL RELATIONSHIP

Cancer And Other Health Outcomes:

- Benzene and acute leukemia
- Benzene and aplastic anemia

SUFFICIENT EVIDENCE OF AN ASSOCIATION

Cancer And Other Health Outcomes:

- Benzene and adult leukemia
- Solvents and acute leukemia
- Propylene glycol and allergic contact dermatitis

LIMITED/SUGGESTIVE EVIDENCE OF AN ASSOCIATION

Cancers:

- Tetrachloroethylene and dry-cleaning solvents and bladder cancer
- Solvents and bladder cancer
- Tetrachloroethylene and dry-cleaning solvents and kidney cancer
- Organophosphorous insecticides and non-Hodgkin's lymphoma
- Carbamates and non-Hodgkin's lymphoma
- Benzene and non-Hodgkin's lymphoma

- Solvents and multiple myeloma
- Organophosphorus insecticides and adult leukemia
- Solvents and adult leukemia
- Solvents and myelodysplastic syndromes

Neurologic Effects:

- Organophosphorus insecticide exposure with OP poisoning and long-term neurobehavioral effects (that is, abnormal results on neurobehavioral test batteries and symptom findings)
- Solvents and neurobehavioral effects (that is, abnormal results on neurobehavioral test batteries and symptom findings)

Other Health Effects:

- Solvents and reactive airways dysfunction syndrome (RADS) which would be evident with exposure and could persist for months or years
- Solvents and hepatic steatosis
- Solvents and chronic glomerulonephritis
- Insecticides and allergic contact dermatitis

INADEQUATE/INSUFFICIENT EVIDENCE TO DETERMINE WHETHER AN ASSOCIATION EXISTS:

Cancers:

- Solvents and oral, nasal, or laryngeal cancer
- Insecticides and pancreatic cancer
- Solvents other than tetrachloroethylene and dry-cleaning solvents and esophageal cancer
- Solvents and stomach, rectal, or pancreatic cancer
- Solvents other than trichloroethylene and mixtures of benzene, toluene, and xylene and colon cancer
- Insecticides and solvents and hepatobiliary cancers
- Insecticides and lung cancer
- Solvents other than tetrachloroethylene and dry-cleaning solvents and lung cancer
- Solvents and bone cancer
- Solvents and melanoma or non-melanoma skin cancer
- Insecticides and soft tissue sarcomas
- Lindane and solvents and breast cancer
- Solvents other than trichloroethylene and cervical cancer
- Solvents and ovarian or uterine cancer
- Insecticides and prostate, testicular, bladder, or kidney cancers
- Specific solvents other than tetrachloroethylene and dry-cleaning solvents and bladder cancer

- Specific solvents other than tetrachloroethylene and dry-cleaning solvents and kidney cancer
- Solvents and prostate cancer
- Insecticides and brain and other central nervous system cancers
- Specific solvents other than benzene and brain and other central nervous system cancers
- Specific solvents other than benzene and non-Hodgkin's lymphoma
- Insecticides and solvents and Hodgkin's disease
- Insecticides and specific solvents and multiple myeloma
- Specific solvents other than benzene and acute and adult leukemia
- Benzene and myelodysplastic syndromes
- Parental preconception exposure to insecticides and childhood leukemias, brain and other central nervous system cancers, and non-Hodgkin's lymphoma
- Parental preconception exposure to solvents and neuroblastoma and childhood brain cancers

Neurologic Effects:

- Insecticides and solvents and peripheral neuropathy
- Insecticides and solvents and Parkinson's disease
- Insecticides and solvents and amyotrophic lateral sclerosis
- Insecticides and solvents and Alzheimer's disease
- Solvents and multiple sclerosis
- Solvents and a long-term reduction in color discrimination
- Solvents and long-term hearing loss
- Solvents and long-term reduction in olfactory function

Reproductive Effects:

- Insecticides and solvents and male or female infertility after cessation of exposure
- Parental preconception exposure to insecticides or solvents and spontaneous abortion or other adverse pregnancy outcomes
- Parental preconception exposure to insecticides or solvents and congenital malformations

Other Health Effects:

- Insecticides and aplastic anemia
- Solvents other than benzene and aplastic anemia
- Insecticides and solvents and irreversible cardiovascular outcomes
- Insecticides and solvents and persistent respiratory symptoms or impairment after cessation of exposure
- Solvents and alterations in liver function tests after cessation of exposure
- Solvents and cirrhosis
- Solvents and chronic pancreatitis and other persistent gastrointestinal outcomes

- Insecticides and solvents and chronic irritant contact dermatitis after cessation of exposure
- Solvents and the systemic rheumatic diseases: scleroderma, rheumatoid arthritis, undifferentiated connective tissue disorders, and systemic lupus erythematosus

LIMITED/SUGGESTIVE EVIDENCE OF NO ASSOCIATION

- No findings