SUMMARY

BACKGROUND

Iraq invaded Kuwait in August 1990. The United States and several other nations responded to this invasion by sending troops to the Persian Gulf. After a period of preparation, these troops fought both an air and a ground war. Hostilities ended in March 1991 after less than three months of combat. The Department of Defense (DoD) has estimated that nearly 700,000 U.S. troops served in Operations Desert Shield and Desert Storm (ODS/DS).

Many veterans of that conflict have reported a range of health problems. The most commonly reported symptoms include joint pains, sleep disorder, memory loss, and fatigue. Some of these symptoms are self-reported more frequently by Gulf War veterans than by persons who did not deploy to the Gulf. These reported health problems are of continuing concern to veterans and policymakers alike. This concern has prompted efforts to evaluate whether exposures of veterans to various risk factors during ODS/DS might be linked to their reported symptoms.

PURPOSE OF THE STUDY

This report is part of the ongoing effort to gain a better understanding of the possible causes of undiagnosed symptoms reported by some ODS/DS veterans. It examines the scientific literature on the potential health effects of pesticides that were present during ODS/DS. A majority of the American troops who served in the conflict probably were exposed to pesticides, including repellents. Although toxicity may vary by individual, improper use of certain classes of pesticides can result in symptoms similar to those reported by some Persian Gulf War veterans (PGWV).

This report reviews literature on 12 of the 35 pesticides that are likely to have been used during ODS/DS. It focuses on these 12 because the Office of the

Special Assistant for Gulf War Illnesses (OSAGWI) considers them to be of potential concern because of either toxicity or expected exposure:

- One organochlorine pesticide (lindane)
- One repellent (DEET)
- Two pyrethroid pesticides (permethrin, *d*-phenothrin)
- Five organophosphate pesticides (azamethiphos, chlorpyrifos, diazinon, dichlorvos, malathion)
- Three carbamate pesticides (bendiocarb, methomyl, propoxur)

This review summarizes reports in the scientific literature of known pesticide exposures or doses and related health outcomes. It should be read in conjunction with two other studies: *Pesticide Use During the Gulf War: A Survey of Gulf War Veterans* (Fricker et al., 2000), a review of the findings from a survey of some 2,000 PGWV regarding patterns of pesticide use during the Gulf War; and *Pesticides Environmental Exposure Report* (OSAGWI, 2000), a report being prepared by OSAGWI that investigates pesticide exposures during ODS/DS and draws conclusions based on all the available evidence.

PESTICIDES EXAMINED

Lindane

Lindane belongs to the organochlorine pesticide class. Few organochlorines are in use today, and lindane has not been produced in the United States since 1977, although it is imported in multiple forms for pharmacological and industrial use. Lindane has been used on a wide variety of insect pests in agricultural, public health, and medicinal applications. However, the U.S. Environmental Protection Agency (EPA) restricts its use, and it can be applied only by certified pesticide applicators.

Two lindane products were shipped to the Gulf, where they were used in dust form during ODS/DS as delousing agents. The primary route of potential exposure in veterans was dermal; lindane can be absorbed efficiently through the skin. The dust formulation used in the Gulf would also make inhalation a feasible route.

Lindane has been used for many years, is well known, and has been extensively studied. Its effects are primarily neurotoxic. Lindane generally produces a rapid response and was designed to increase insect respiration to lethal levels. Acute human exposure can result in neurologic changes, including hyperexcitability, tremor, seizure, and coma. The symptoms are generally reversible

with supportive care, although ingestion of large amounts of lindane has resulted in death. Epidemiologic studies in the literature also suggest the possibility of subtle long-term neurologic and reproductive health effects; however, subjects in these studies were exposed to a number of different potentially toxic substances, making it difficult to attribute findings specifically to lindane.

Acute human exposure has usually resulted from accidents either in the manufacture of lindane or in its application in agricultural settings. Acute symptoms reported in humans exposed to lindane include headache, nausea, vomiting, restlessness, ataxia (loss of muscular coordination), tremor, and excitability. Seizure has been reported with more extensive exposures, although specific levels at the times of exposure are not reported.

Few studies specifically evaluate the effects of chronic dermal exposure to lindane, since the intended use of lindane for treating parasitic infection (e.g., lice) generally requires only a single application. However, some studies document human hematological manifestations, including bone marrow hypoplasia and aplastic anemia, following prolonged dermal exposures.

Individuals employed in the manufacture of lindane are exposed to a combination of hexachlorocyclohexane (HCH) isomers (chemical forms) with different effects in biological systems. (Lindane is the gamma isomer.) Humans are also exposed to lindane as an environmental toxicant. Lindane has been used in vaporizers and included among other chemicals in wood preservatives and has been used as an agricultural pesticide. Some situations have precipitated unintentional prolonged exposures to low levels of lindane in the environment. Reports in the literature are either anecdotal or of an epidemiologic case-control nature, where subjects may have been exposed to a number of chemical toxicants simultaneously, making it difficult to attribute specific effects to individual chemical exposures.

Because of the potential risks associated with lindane, its use is no longer recommended as the first-line drug therapy for treating scabies and body lice. Although it should be used with caution, when used appropriately, lindane is generally considered a safe and effective pesticide.

DEET

N,N-Diethyl-*m*-toluamide, also known as DEET, is an aromatic amide that repels a wide range of insects. DEET was first developed by the U.S. Department of Agriculture for military use in 1946, and it has been estimated that approximately 38 percent of the U.S. population uses DEET-containing repellents annually. DEET insect repellent is part of a complete repellent system used by U.S. military personnel. Three different DEET products were shipped to the

Gulf, where they were applied to the skin in cream, liquid, or stick forms. Until 1989, the standard-issue insect repellent of the U.S. military consisted of 75 percent DEET in an alcohol base. This has been replaced with a slow-release, polymer-based product containing 33 percent DEET, which is also available to the general public.

DEET can enter the body through several pathways, including dermal and ocular exposures, inhalation, and ingestion. It is an ideal permeant of skin and has been reported to accelerate the dermal penetration of pharmaceuticals, raising the concern that DEET may also increase dermal penetration of pesticides, since they are often used together. Uncertainty about how much DEET humans absorb complicates any assessment of effects. Generally, the magnitude of DEET that permeates the skin is closely related to the repellent formulation.

Animal studies have shown DEET to affect the cardiovascular and nervous systems. As with many pesticides, the majority of health effects reported to be caused by DEET result from acute exposure. In fact, no evidence in the literature suggests that chronic low-level exposure to DEET will result in long-term effects (with the exception of rare reports of scarring). Therefore, there is no evidence to suggest such a scenario is of great concern in predicting the potential health effects of DEET on PGWV.

Most reviews of DEET toxicity conclude that the risk of adverse effects from the use of DEET-containing repellents as directed by the label appears low. This conclusion is based on reviews of human effects reports, animal toxicology, and possible alternate etiologies for symptoms reported in most patients. In fact, hypersensitivity may be required for severe acute toxic effects to occur, and a suite of data from animal studies generated to support DEET registration provides no evidence of adverse long-term effects related to DEET exposure. Generally, patients who are reported to present severe symptoms related to DEET use recover without reported further effects.

A correlation between the concentration of DEET in a repellent and the frequency or severity of effects is not supported by the literature. Further, it is difficult to quantify consistently the temporal relationship between the onset of central nervous system (CNS) symptoms and exposure to DEET, but the reaction is generally rapid, as is the resolution in most cases. There have been relatively few severe adult effects related to DEET exposure. While a pattern of potentially severe neurotoxicity in children who have been exposed to DEET is emerging, the total number of reported cases is very small compared with the population exposed. This pattern has not been observed in adults. The reasons for this disparity are unknown but may relate to a different surface-area-to-volume ratio in children than in adults.

Concern about the interactive effect of DEET with other chemicals may be warranted, but the available literature is not adequate to permit definitive conclusions at this point. As difficult as it is to extrapolate the results of animal studies to long-term human effects, the presence of chemical interactions compounds the uncertainty inherent in this process. This is not to say, however, that further research should not be undertaken. A prudent approach may be first to determine more accurately which exposures warrant further study. Research to explain the broad variety of outcomes associated with DEET exposure may also be warranted, especially to explain cases of hypersensitivity.

Pyrethroids

Pyrethroids are synthetic pesticides based on the pyrethrins, which are derived from chrysanthemums. Pyrethrins are a "natural" environmental product that is of low toxicity to mammals. They degrade quickly in sunlight, and the cost of reapplying them has limited their widespread agricultural use. Pyrethroids have been synthesized to be similar to pyrethrins but more stable in the environment. Some commercial pyrethroid products also contain organophosphate (OP) or carbamate insecticides because the rapid paralytic effect of pyrethrins on insects is not always lethal. Pyrethroids are formulated as emulsifiable concentrates, wettable powders, granules, and concentrates.

Two pyrethroid pesticides are of interest in the Gulf War setting: permethrin and *d*-phenothrin. As part of the DoD Insect Repellent System, permethrin was issued in ODS/DS as a ready-to-use insect repellent labeled for use on clothes such as the battle dress uniform (BDU) and bed netting. The second compound, *d*-phenothrin, is an indoor-use aerosol insecticide, used most commonly for spraying bed netting (to kill insects trapped inside after installation) or spraying inside aircraft to prevent transport of insects.

The literature discussing permethrin stresses its relative safety. Individuals with occupational exposure have been reported to experience facial skin sensations (burning or itching), usually within a few hours of exposure. Ingestion of permethrin has resulted in epigastric pain, nausea, and vomiting. Acute poisoning symptoms relate primarily to the effects of pyrethroids on the nervous system and include dizziness, headache, nausea, anorexia, and fatigue. Very large exposures cause muscle fasciculation and altered consciousness.

After permethrin was introduced as an alternative treatment for head lice in humans, data were gathered regarding possible adverse effects. Approximately 2.2 adverse events were reported per 1,000 administrations. These events, although perhaps underreported, were not clinically serious. The most common

ones were itching and a rash. Other effects (e.g., shortness of breath, gastrointestinal effects) occurred in a few patients.

Data on chronic human exposure to permethrin come primarily from studies of pest-control workers and clinical evaluation of patients treated for scabies and lice infestations. Data again support the conclusion that permethrin is extremely safe when used in conventional applications. Furthermore, reproductive studies do not show any attributable adverse impact from fairly high doses of permethrin. Animal studies of subacute and chronic exposure, even at high doses, generally fail to show any lasting effects. Only at extremely high doses do animals begin to demonstrate evidence of neurologic impairment.

We uncovered few references for *d*-phenothrin. Those that were available repeatedly address the relative safety of this insecticide and the pyrethroids in general. The effects of *d*-phenothrin on animals include acute toxicity but only at extremely high doses and in routes inconsistent with conventional exposure of humans. Similarly, studies of the chronic effects of *d*-phenothrin on animals show toxicity but only at extremely high oral doses. Even at these high exposures, reproductive, genetic, and carcinogenic effects were not observed. The literature does not provide evidence of *d*-phenothrin toxicity to humans.

Pyrethroids, particularly permethrin and *d*-phenothrin, are safe and effective when used in recommended applications. Studies show that these compounds are potentially toxic at extremely high exposures; however, when used in conventional ways, only minor skin irritation in sensitive individuals results, and the irritation subsides after short periods when the irritant is removed.

Organophosphates

Organophosphate Compounds. Organophosphate (OP) compounds were first synthesized in significant amounts during the 1940s, when tetraethylpyrophosphate was developed as an insecticide.

Azamethiphos is an OP pesticide that was probably procured locally during ODS/DS as a fly bait. It has been used in Canada, Scandinavia, the United Kingdom, and France to control sea lice infestations and in Mexico, primarily for fly control. Commercially available azamethiphos products include Alfacron 10 and Snip. Alfacron 10 is used as a wettable powder, and Snip is a 1 percent azamethiphos granular fly bait. Both were reported to have been used during ODS/DS, and both were probably obtained locally.

Chlorpyrifos is a broad-spectrum insecticide. It is registered for a variety of uses and sites and is effective in controlling cutworms, corn root worms, cock-

roaches, grubs, flies, termites, and fire ants. It is available in a variety of formulations, including granules, wettable powder, dustable powder, and emulsifiable concentrate.

Diazinon is an insecticide used to control cockroaches, silverfish, ants, and fleas in buildings. Diazinon is also commonly used in home gardens and on farms to control a wide variety of sucking and leaf-eating insects. It is available in dust, granules, seed dressings, wettable powder, and emulsifiable solution formulations.

Dichlorvos is effective against flies, aphids, spiders, and caterpillars. It acts against insects as both a contact and a stomach poison. Dichlorvos is used as a fumigant and has also been used to make pet collars and pest strips.

Malathion is a wide-spectrum insecticide. It is used to control sucking and chewing insects on fruits and vegetables and also to control mosquitoes, flies, household insects, and animal parasites. During ODS/DS, malathion was primarily intended for use as an outdoor spray to control mosquitoes and flies.

Potential Health Effects of Organophosphates. OP agents bind to and inhibit the normal action of acetylcholinesterase (AChE), an enzyme. Acetylcholine (ACh) is a major nerve-signaling chemical that acts as a chemical messenger both in the brain and elsewhere in the body. AChE serves a critical role in regulating nerve signaling to other nerve cells or to muscle cells. When AChE is inhibited by an OP, an excessive accumulation of ACh occurs in the synapse, followed by excessive binding of ACh to the receptors on the receiving cell. Consequently, cells are excessively stimulated.

In cases of toxicity from OP exposure, symptoms can range from mild tremors to more severe muscle contractions, impaired cognition, dizziness, shortness of breath, and vomiting. In severe cases, respiratory failure and death can result. Other effects include excess secretions (sweating, tearing, and salivation), bradycardia, miosis, insomnia and sleep abnormalities, headaches, dizziness, effects on mood (depression and anxiety), effects on personality (aggressiveness, irritability, and paranoia), effects on cognition (confusion, and enhancements and reductions in measures of attention, concentration, memory, learning, and psychomotor speed), tremor, ataxia, dysarthria, hypotension, respiratory depression or arrest, convulsions, and coma.

The severity of acute symptoms relates to the amount and route of exposure. There were no systematic reports in the literature of acute toxicity resulting from any pesticide exposures during ODS/DS. For this reason, this report focuses primarily on chronic exposures and long-term effects, as chronic health effects are of greater relevance to Gulf War illnesses.

As with other pesticides, most of what is known about the effects of persistent OP exposure in humans is based on observational studies. These studies are usually focused on occupational exposures, and they commonly involve a mixture of pesticides and possibly other compounds. Many of the studies involve assessing symptoms of a study group that is exposed to pesticides seasonally. Further, a combination of acute and chronic exposures and effects is often present, and this combination is usually undefined. Other knowledge is gained from case reports, many of which involve household pest control. These types of studies were reviewed for the reported ranges of chronic symptoms associated with OP exposure, including fatigue, joint and muscle symptoms, sleep effects, headaches, skin effects, cognitive effects (memory loss, confusion), mood effects, and neurological effects. These classes of symptoms are also seen frequently in ill PGWV.

Carbamates

Carbamate Compounds. The use of carbamates as insecticides began in the 1950s, and approximately 25 carbamate compounds are in use today as pesticides or pharmaceuticals. Carbamates are among the most popular pesticides for home use, both indoors and on gardens and lawns.

Bendiocarb is a broad-spectrum insecticide used to control disease vectors, such as mosquitoes and flies, and household and agricultural pests. Most formulations of bendiocarb are registered for general use, except for Turcam and Turcam 2.5G, which are restricted products. Perhaps the best known bendiocarb product is Ficam. Formulations include dusts, granules, ultra-low-volume (ULV) sprays, and wettable powders. Bendiocarb was primarily available during ODS/DS as a wettable powder for indoor surface treatment.

The EPA classifies *methomyl* as highly toxic to humans and restricts its use. Methomyl was introduced in 1966 as a broad-spectrum insecticide and was first registered in 1968. It was re-registered in 1998, with the U.S. EPA concluding that methomyl products did not pose unreasonable risk to humans or the environment when labeled and used correctly. Methomyl can be formulated as a wettable powder, a soluble concentrate or liquid, a dust, or a solid bait. It was intended to be used exclusively as a fly bait during the Gulf War.

Propoxur was introduced in 1959 as an insecticide, and it was first registered in the United States in 1963. Like methomyl, it has both contact and systemic activity against insects and is used on a variety of pests in both agricultural and other applications. Propoxur is a general-use pesticide, although some formulations may be for professional use only. Propoxur is characterized as having a fast knockdown and long residual effect, which makes it a popular choice for pest control. It is used primarily indoors, with limited outdoor applications.

Propoxur is available in a variety of formulations, including emulsifiable concentrate, wettable powder, dustable powder, granules, aerosol generator, smoke generator, and baits. During ODS/DS, propoxur (Baygon) was available to control pests in cracks and crevices (e.g., cockroaches) and could also be sprayed on building surfaces and screens to control pests outdoors.

Potential Health Effects of Carbamates. Carbamates have the same presumed primary mechanism of toxicity that characterizes OPs: They are AChE inhibitors. For this reason, OPs and carbamates are often considered together. But whereas OPs irreversibly inhibit AChE, requiring more enzyme to be produced for function to be restored, carbamates inhibit the enzyme reversibly. The body of literature regarding the acute and chronic effects of carbamates is largely covered in the discussion of OPs.

Symptoms found to occur following exposure to AChE inhibitors such as OP and carbamate pesticides include fatigue, joint and muscle symptoms, sleep effects, headaches, skin effects, cognitive effects, mood effects, and neurological effects. These classes of symptoms are also seen frequently in ill PGWV.

CONFOUNDING FACTORS

Part of the difficulty in evaluating possible effects of pesticides on PGWV is that a number of factors confound the evaluation. Primary among these are the inherent differences among individuals and potential interactions among pesticides and other influences, including drugs and the environment.

Individual Differences

A number of individual differences complicate the analysis of the effect of pesticides on PGWV. First, genetic differences occur among individuals. For example, DEET is potentially more toxic to people with genetic or acquired defects in ammonia metabolism, such as carriers of ornithine carbamoyl transferase (OCT) deficiency. Second, many factors may affect the rate and magnitude of pesticide absorption. Protective clothing and differences in skin properties and integrity influence dermal exposure, and inhalation exposure may vary with ventilation or as a result of other factors, including properties of airway membranes. Furthermore, the rates at which pesticides are cleared depend on amounts, genotype, and activity of enzymes involved in their metabolism. Some evidence points to differences in metabolizing enzymes among PGWV. Finally, individual differences in cofactors that modify the effect of pesticides, are essential for metabolism of pesticides, or permit or inhibit toxic effects by pesticides may contribute to differences in clinical effects. Such cofactors can include vitamins C and E, phytochemicals, and cholesterol.

Interactions

Pesticides in combination with other factors may exert effects different from those experienced with pesticides alone. Moreover, effects from two pesticides may differ from those expected from exposure to either separately. It is not feasible to predict the toxicity of pesticide mixtures (or pesticides in combination with other exposures) on the basis of the results of the toxicity of single compounds. Moreover, the number of possible combinations increases exponentially with the number of agents as 2^n; thus, 10 compounds have more than 1,000 possible combinations that could have different consequences. The effects of interactions may be additive, synergistic, or antagonistic, and the character of the interactions may differ for different effects of the compounds.

Nevertheless, it is possible that multiple exposures to pesticides and other compounds occurred during ODS/DS, underscoring the need to further investigate the nature of these potential exposures. Some data are available on interactions of substances relevant to ODS/DS, including interactions among DEET, pyridostigmine bromide (PB) (a carbamate drug given to protect against nerve agents), and pesticides; among pyrethroids, OPs, and carbamates; and among pesticides and drugs or other exposures.

DEET has been reported to enable other chemicals to penetrate the skin more easily. A scenario involving a soldier using DEET, wearing a uniform treated by permethrin, and taking PB is quite plausible. Data concerning the combination of DEET, PB, and pesticides show a greater-than-additive effect when two or three of the chemicals are present. However, the doses used in the studies of these combinations were exceptionally high. For example, in one study, a 160-pound subject would have to take 467 PB tablets and apply 76 tubes of a 33 percent DEET solution to achieve an equivalent exposure. These levels make it difficult to understand the implications for health effects at much lower levels. However, the increased effect demonstrated when the compounds are used in combination indicates that this phenomenon warrants further attention.

Effects on the ACh system constitute one mechanism by which interactions of pyrethroids with OP and carbamate pesticides may occur (other mechanisms of interaction are also possible). Some animal studies have found pyrethroids in the fat and brain of exposed subjects and in poisoned cotton sprayers, so the possibilities of interactions occurring even with a delay following pyrethroid exposure remain a concern.

One report on PB characterizes interactions between that carbamate and heat, stress, caffeine, nicotine, and antihistamines. Because other carbamates, as well as OPs, share PB's major pharmacological effect (AChE inhibition), the data on potential interactions with these agents also have bearing. The use of PB in

combination with an OP pesticide may have a novel effect on central ACh regulation.

Environmental factors also complicate the analysis of effects. Heat may affect the blood brain barrier, and it also affects acetylcholinergic nerve terminal function. It may increase the quantity of ACh released, potentially exacerbating the effect of AChE inhibitors. Antihistamines also have potential cholinergic effects, so interactions between antihistamines and OP/carbamate pesticide exposure might also be anticipated.

Other potential interactions of interest involve diet, alcohol, and diet supplements. Studies in rats have demonstrated that diet can affect susceptibility to the adverse effects of pesticides. Possible mechanisms of interaction among pesticides that relate to diet and alcohol intake include membrane effects. Because alcohol affects membranes, it cannot be excluded as an exacerbating factor. Studies have shown protective effects by antioxidant vitamins on lipid peroxidation and oxidative damage, which OP agents have been shown to cause; however, it should be noted that the dose of vitamin may determine whether it has primarily a prooxidant or an antioxidant effect.

CONCLUSIONS

A review of the scientific literature is but one step in determining the potential contributions of pesticides to the symptoms reported by some PGWV. Although it can assist in developing essential hypotheses, such a review cannot itself completely substantiate or repudiate a causal link between pesticide use and illness. To date, estimations of exposure and degree of PGWV illness have relied heavily on self-reported evidence, a method with several important limitations. It is hoped that this review will provide relevant information about the potential human health effects of pesticide exposure at levels reported in the literature, and that this information will be useful in subsequent efforts to further characterize the role, if any, of pesticides in Gulf War illnesses.

Where possible, the review focuses on reports in the scientific and medical literature that may be relevant to symptoms reported by some PGWV. There were no identified reports of acute exposure to pesticides that resulted in toxicity severe enough to cause PGWV to seek medical treatment during ODS/DS. The body of literature that is most informative therefore focuses on long-term, chronic human effects of reported pesticide exposures. Specific attention has been paid here to OP and carbamate pesticides, because the literature contains more breadth and depth in research and clinical findings related to the role of these AChE inhibitors in long-term, chronic effects, which are most relevant to Gulf War illnesses. The literature related to the other classes of pesticides lacks this robustness, in some cases due to a paucity of

research, but more often because long-term human effects have not been consistently observed.

The central question, of course, is whether the scientific literature suggests that pesticides could contribute to health problems reported by PGWV. Evidence in the literature is suggestive, but not conclusive, that pesticides, specifically AChE inhibitors such as OPs and carbamates, could be among the potential contributing agents to some of the undiagnosed illnesses seen in PGWV. Potentially supportive evidence exists in the areas of epidemiology, genetic and biological differences between ill and healthy subjects, physiological mechanisms of AChE inhibitors, and similarities between clinical findings of AChE inhibitor-exposed subjects and reported symptoms among PGWV. Clearly, significant uncertainties remain, especially in linking these lines of evidence with actual exposures to AChE inhibitors (including pesticides) during ODS/DS. It is also clear that more research is needed to confirm or refute a causal link between pesticides and other agents and illness among PGWV. No prospective studies have been conducted that positively identify pesticides as causative agents of the symptoms associated with Gulf War illnesses.

While further research can provide ever stronger evidence about the role of AChE inhibitors such as pesticides in the genesis of illness, such lines of inquiry may not provide independent identification of all the causes of illnesses in PGWV. This is especially true if several—or even many—causes of illness exist that are possibly interactive and manifested differently among individuals. Clearly, such approaches can be made more promising with increasing knowledge of actual exposure to potential causative agents, including pesticides, during ODS/DS.

Although the scientific literature has implicated exposure to AChE-inhibiting chemicals (including some pesticides) as a contributing factor in several well-defined conditions, including some health problems similar to some experienced by PGWV, few problems or symptoms are uniquely characteristic of pesticide exposure. Given the evidence to date and the literature reviewed, it is inappropriate to rely upon exposure to pesticides, especially OPs and carbamates, as the explanation for the myriad health problems reported by PGWV; however, we think it equally inappropriate at this point to completely rule out pesticides as a potential contributing factor. It is clear that more research will be necessary to further define any potential role that pesticides may have played in causing undiagnosed illnesses seen in PGWV.