

GENERAL COMMENTS

This review of the scientific literature on specific pesticides that were identified by OSAGWI as pesticides of concern for their possible causal relationship with some of the undiagnosed illnesses seen in PGWV is intended to complement other ongoing studies, including a companion RAND project that surveyed PGWV to determine patterns of pesticide use during the Gulf War (Fricker et al., 2000). A forthcoming OSAGWI report will investigate pesticide exposures and draw conclusions based on all the available evidence.

While a review of the scientific literature can be used to develop essential hypotheses, it cannot completely substantiate or repudiate a causal link between pesticide use and illness; other factors such as actual exposure to pesticides are crucial in such a determination. To date, estimations of exposure and degree of illness have relied heavily on self-reports by PGWV. This method has several serious limitations, which have been considered and discussed in this report. The information about the potential health effects of pesticide exposure at levels reported in the literature should be useful in subsequent efforts to further characterize the role, if any, of pesticides in Gulf War illnesses.

Where possible, we have focused on reports 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 most informative literature focuses on long-term, chronic effects of reported pesticide exposures on humans. In our review, we paid particular attention to OP and carbamate pesticides, since more research and clinical findings are available concerning the role of these AChE inhibitors in long-term, chronic effects. The literature on the other classes of pesticides lacks this robustness, in some cases due to a paucity of research, but more often because long-term effects on humans have not been

consistently observed. Furthermore, previous research into PB, a carbamate used in ODS/DS for nerve-agent prophylaxis, provides some evidence of a possible role of AChE inhibitors in long-term effects similar to those experienced by some PGWV.

THE POSSIBLE CONTRIBUTION OF PESTICIDES TO HEALTH PROBLEMS REPORTED BY PGWV

The evidence in the literature is suggestive, but not conclusive, that pesticides, specifically AChE inhibitors, 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, there are significant uncertainties, especially in linking these lines of evidence with actual exposures during the PGW. It is also clear that more research is needed to confirm or repudiate a causal link between pesticides (as well as other agents) and illness among PGWV. No prospective studies positively identify pesticides as causative agents of the symptoms associated with Gulf War illnesses. Recommendations for such research have been made in syntheses throughout this report, however, and are also reiterated below.

Epidemiology

Despite the uncertainties of findings in the body of epidemiological research (see Chapter Three), the literature reports putative associations between perceived pesticide exposure and increased development of chronic multisystem illness in PGWV. Several studies from the United States and the United Kingdom have shown a link between self-reported pesticide exposure and illness. Although these studies are subject to the limitation that pesticide exposure was measured by self-report, at present there has been no better measure for pesticide exposure during the PGW. However, there is insufficient evidence to clearly define a causal link between self-reported pesticide exposure and increased likelihood of illness. If the existence of a causal link is to be adequately examined, it will be necessary to conduct studies with replications of the samples reviewed in Chapter Three. It is hoped that concurrent and subsequent studies will provide better measures for pesticide exposure during the PGW so that the reported epidemiological research can be critically revisited.

Individual Differences

Explanations for why some PGWV report illness and others do not may include differing exposures to causative agents and differing manifestations of these exposures among individuals. The issue of differing exposures is difficult to resolve due to a necessary reliance on self-reports of exposure, especially in view of the time passed since the PGW. However, the pesticide literature emphasizes the importance of individual differences in susceptibility (e.g., Leng and Lewalter, 1999). These differences can play a pivotal role in determining rates of metabolism and clinical toxicity of AChE-inhibiting agents.

Individual susceptibility to the effects of pesticides, particularly AChE inhibitors, can vary widely. The differences arise from

- Genetic differences in enzymes that contribute to metabolism and clearance of AChE inhibitors.
- Biological differences in activity of enzymes, even those enzymes whose genetic character is similar. (These differences are determined by a host of factors, some of which are environmental and many of which are unknown.)
- Other factors that influence the effect of AChE inhibitors in the body (e.g., baseline neurochemical status, itself defined by genetic and environmental factors, and membrane function, in turn determined by factors such as genetics and diet).

That these individual differences have a role in the genesis of illness is a priori likely. Some individuals exposed to certain environmental conditions became ill, while others exposed to apparently similar conditions did not. Moreover, the manifestations of illness are not completely uniform.

The finding that there are significant differences in both genetic type and activity of enzymes involved in sequestering and metabolizing AChE inhibitors between ill PGWV and healthy controls suggests a possible contribution by AChE inhibitors to reported illnesses in PGWV. The degree to which this may reflect reactions to PB rather than to carbamate and OP pesticides cannot at present be ascertained.

Future studies could seek to replicate findings of reduced activity of AChE-inhibitor detoxifying enzymes (perhaps adding chlorpyrifos oxonase and other arylesterases to the examined set) and to replicate findings of increased prevalence of low-metabolizer enzymes (K-variant, Florida variant, atypical BuChE, and paraoxonase isoforms) in ill PGWV. Studies might also focus on other factors, such as serum cholesterol and membrane fatty-acid composition, as well

as membrane fluidity, which may serve as additional cofactors in susceptibility to AChE-inhibitor effects. Further studies that evaluate whether factors like membrane fluidity or membrane composition and neurotransmitter receptor expression systematically differ between ill PGWV and controls would also be useful. The findings could serve as markers of prior susceptibility and/or as markers of chronic effects induced by OP exposure.

Interactions

There is evidence in the literature that pesticides, particularly AChE-inhibiting OPs and carbamates, may interact with—i.e., have their impact modulated by—a wide variety of conditions, including heat, foods and food constituents, recreational drugs, and pharmaceutical agents. These interactions themselves can be complicated by individual factors such as genetic differences in metabolizing enzymes, as discussed above. The differences in interacting factors are such that persons with the “same” AChE-inhibitor exposure may experience widely varying consequences. Future research could be vitally important for defining which factors and coexposures should be avoided or sought in future circumstances involving exposure to AChE-inhibiting pesticides, in both military and civilian populations. Such research is strongly recommended.

Biological Plausibility and Clinical Evidence

Evidence from the AChE-inhibitor literature suggests that administration of AChE inhibitors may lead to changes in ACh regulation beyond the obvious short-term reduction in ACh breakdown. Some of these changes resolve following cessation of exposure, at least in most of the cases studied; but other changes are long-lasting and perhaps permanent, and they may allow for indefinite changes in the regulation of ACh. Moreover, other factors (including greater age and prior exposure) may impair recovery even for those domains that might normally be fully restored.

ACh is important in the regulation of pain, sleep, muscle function, skin function, cognition, and mood—areas that figure prominently in complaints of ill PGWV. Thus, symptoms of the type seen in ill PGWV could plausibly be produced by changes in the regulation of ACh induced by exposure to AChE inhibitors. This inference offers some suggestion that AChE inhibitors, possibly including OP and carbamate pesticides, may have a role in illness in PGWV; however, it in no way precludes an important additional role of other non-AChE-inhibiting exposures.

Representative similarities in symptoms and clinical findings for ill PGWV and persons exposed to AChE-inhibiting agents are presented in the Appendix.

Compelling similarities exist in the symptom categories of fatigue, muscle and joint pain, headaches, chemical sensitivity, skin and hair effects, cognitive problems, and sleep disturbances. Apparent similarities exist both in the symptoms that are reported and in many classes of problems that are not. However, it is possible that looking at these symptoms more carefully will reveal differences between the groups; for example, the apparent similarities might turn out to be the artificial result of categorization of different “sleep” symptoms under one rubric.

The specificity of the similarities can also be questioned. It is possible that other classes of exposures might produce a similar constellation of symptoms. Exposures to organic solvents may produce symptoms most closely approximating those here, although the similarities may result in part from similar mechanisms (such as alteration in receptor expression). Although these agents do not “fit” all other identified data, such as genetic polymorphisms in enzymes that metabolize AChE inhibitors, and there is no strong reason to suppose that PGWV had greater exposure than other persons to organic solvents, an adjunctive role for organic solvents—as for other interactants—cannot be excluded. In short, there are unlikely to be many agents that would produce such similar effects in terms of both symptoms reported and symptoms and signs not present.

It would also be useful to examine the conditions that have been treated successfully by ACh-promoting drugs and the concordance between these conditions and symptoms in ill PGWV. If downregulation occurs (or if it predominates) following exposure to AChE inhibitors, then drugs that raise ACh action might lead to benefit. A sense of what the symptoms of ACh downregulation might be can be gained by examining those that have been shown to derive benefit from ACh augmentation (looking outside the PGWV setting). Insofar as there is agreement between symptoms treated by stimulating the ACh system outside the PGWV setting and symptoms reported by PGWV, a connection between ACh downregulation and illness is tentatively supported. ACh agents have been used to treat fatigue and muscle weakness (Rustam et al., 1975; Trojan and Cashman, 1995a,b; Braham, 1994), memory and cognitive problems (Gray et al., 1996), diarrhea (in the special case of ulcerative colitis), Parkinson's disease, sleep apnea (Benowitz, 1996), and pain (Damaj and Martin, 1996; Donnelly-Roberts et al., 1998). Ill PGWV commonly report fatigue and muscle weakness, memory and cognitive problems, diarrhea, and sleep apnea. These data too are consistent with a possible role of ACh depression in illness in PGWV, as might be expected following AChE-inhibitor exposure.

In summary, a number of classes of symptoms have been identified in both individuals exposed to AChE inhibitors and ill PGWV. Additional data are re-

quired to further evaluate these observations, since the available research has significant limitations:

- Most studies of AChE-inhibitor exposure in humans are observational in nature, although it would probably be difficult to randomize persons exposed to OP or carbamate pesticides or persons employed in jobs entailing such exposure. Many studies are small and poorly controlled.
- Existing research on pesticide formulators and applicators is limited by the use of subjects who remain in occupations that entail exposure; this may select for the most resilient subpopulation. Those most affected may have selected themselves out of this field, through illness or intolerance.
- No identified studies entail true pre-exposure measurements: We found no prospective research that examined pesticide applicators or pesticide formulators prior to initial employment in this field and again during and after employment, compared with controls matched for age, gender, baseline intelligence and education, and other pertinent factors, tested at similar times. Such research is clearly needed.
- Few studies of OP- and carbamate-pesticide-exposed persons have systematically assessed symptoms. One study did so in a review-of-systems fashion, finding that exposed individuals scored higher in many classes of symptoms than did non-exposed comparators. This is important information and would be useful to replicate a longer time after exposure. The findings would be still more useful if more specific information within symptom categories was also elicited. A detailed cataloging of symptoms and of the comparative frequency of symptoms would be useful to enable a comparison with PGWV.

Also needed are additional studies of specific objective measures that may be changed in ill subjects with prior AChE-inhibitor exposure. Some such studies have been done, but few are well replicated or entail large samples, nor do they provide comparisons of different exposures within and outside the OP and carbamate pesticide classes.

CONCLUDING OBSERVATIONS

Evidence of the biological plausibility of AChE inhibitors as a potential cause of symptoms similar to those reported by ill PGWV suggests that these compounds could be among the potential contributing agents to some of the undiagnosed illnesses seen in PGWV. However, reliable conclusions about the possible contribution of pesticides cannot be drawn from consideration of the range of symptoms suffered by ill PGWV, although findings of relevant individual

differences among PGWV who report illness and those who do not provide additional evidence about the possible role of AChE inhibitors.

Pesticide use is so ubiquitous that studying the effect of human exposure to low-level pesticides is “difficult to investigate because of the problem of finding a pesticide-free control population” (Longo, 1980). Nevertheless, new information continues to change scientists’ perception of the potential health effects of these chemicals. For example, it has been reported that the EPA will soon reduce the acceptable exposure limit for chlorpyrifos by 90 percent, based on reported brain damage in fetal rats whose mothers were exposed (*Washington Post*, June 1, 2000, p. A1). While further research can similarly provide new, stronger evidence about the role of AChE inhibitors in the genesis of illness, such lines of inquiry may not independently identify 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, however, 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 various well-defined conditions, few health 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. To do so without additional research would ignore the observed similarities between undiagnosed illnesses seen in PGWV and health effects associated with pesticide exposure. It is clear that more research will be necessary to further define any causative role that pesticides may have played in the undiagnosed illnesses of PGWV.

