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Suicide and Exposure to Organophosphate Insecticides: Cause or Effect?

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Background *Suicide using pesticides as agent is recognized as a major cause of pesticide poisoning.*
Methods *A literature review of mortality and morbidity studies related to suicide among pesticide-exposed populations, and of human and animal studies of central nervous system toxicity related to organophosphate (OP) pesticides was performed.*
Results *Suicide rates are high in farming populations. Animal studies link OP exposure to serotonin disturbances in the central nervous system, which are implicated in depression and suicide in humans. Epidemiological studies conclude that acute and chronic OP exposure is associated with affective disorders. Case series and ecological studies also support a causal association between OP use and suicide.*
Conclusions *OPs are not only agents for suicide. They may be part of the causal pathway. Emphasizing OPs solely as agents for suicide shifts responsibility for prevention to the individual, reducing corporate responsibility and limiting policy options available for control.* Am. J. Ind. Med. 47:308–321, 2005. *© 2005 Wiley-Liss, Inc.*

KEY WORDS: organophosphates; suicide; depression; impulsivity; serotonin, causation; policy

INTRODUCTION

Pesticide poisoning is a serious problem among developing country populations, particularly in rural agricultural areas, where pesticide usage is widespread and where access to pesticides is poorly controlled [Jeyaratnam, 1990; World Health Organization and United Nations Environment Program, 1990; Forget, 1993; He et al., 1999; Ecobichon, 2001; Dinham and Malik, 2003; Gunnell and Eddleston, 2003]. World Health Organization (WHO) estimates, now almost two decades old, cite a figure of 1 million unintentional and 2 million intentional poisonings per year, with 220,000 deaths [World Health Organization and United Nations Environment Program, 1990]. Despite uncertainty about the accuracy of various models used to make such estimates [Levine and Doull, 1992; McConnell et al., 1993], the numbers are sufficient to confirm the existence of a major public health problem [Jeyaratnam, 1990].

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The Global Epidemiology of Pesticide Poisoning and Patterns of Causation

Epidemiological studies of pesticide poisoning usually indicate three main categories of circumstances under which poisoning occurs, viz. occupational exposures resulting in occupational accidents, intentional exposure (suicide and attempted suicide), and non-occupational accidental exposures (such as domestic accidents). In many reviews and empirical studies, suicide is cited as the major cause of pesticide poisoning, exceeding occupational exposures, and non-occupational accidents by a factor of four or more in many countries (Table I).

Jeyaratnam [1990] estimated that there are about 2 million suicide attempts involving pesticides in the world annually. Percentages of hospital admissions for pesticide poisoning attributable to suicide in Sri Lanka have ranged from 36% in 1983 [Jeyaratnam et al., 1987] to 68% for 1991–1994 [Van der Hoek et al., 1998] and 73% in both 1979 [Jeyaratnam et al., 1982], and the period from 1975 to 1983 [de Alwis and Salgado, 1988]. Gourmelon [1999] found that over 90% of pesticide-related admissions to two hospitals over 4 months in Sri Lanka were due to suicide in 1996/1997. Similar high estimates of the proportion of suicide among pesticide poisoning admissions have been reported in Malaysia (68%), Indonesia (63%), and Thailand (61%) [Jeyaratnam et al., 1987] and in India (75%) [Gourmelon, 1999]. The percentage of pesticide poisoning notifications due to suicide reported to the Ministry of Health was 49% in Malaysia, 64% in Philippines, 50% in Thailand [Lum et al., 1993], and 74% in Hong Kong [Chan et al., 1996].

Suicide, therefore, appears as the most important cause of pesticide poisoning in the East. By the 1990s, suicide using aluminum phosphide had become so common in Northern India [Banjar and Wasir, 1990; Siwach and Gupta, 1995] that respirators were being routinely worn for protection at suicide autopsies in Indian hospitals [cited in Levine and Doull, 1992]. Not surprisingly, recent reviews have called this problem of intentional ingestion of pesticides a ''continuing'' and ''overlooked tragedy'' in the developing world [Eddleston et al., 1998; Gunnell and Eddleston, 2003].

In Africa, anecdotal reports also cite suicide as the major reason for pesticide poisoning in Tanzania [Ngowi et al., 1992], Kenya [Mbakaya et al., 1994], and Zimbabwe [Baloyi, 1989]. Reviews in teaching hospitals in Harare attributed 73% [Nhachi, 1988] and 85% [Loewenson and Nhachi, 1996] of hospital admissions for pesticide poisoning to suicide. Suicide constitutes the largest cause for pesticide poisonings notifications (about 35–40%) in South Africa [London et al., 1994; Department of Health, 1995].

On the other hand, reports from South and Central America provide lower estimates of the proportion of pesticide poisonings due to suicide. For example, Cole et al. [2000] found that only 16% of cases detected with intensified passive surveillance in a potato farming area of Ecuador in 1991/1992 were due to suicide. Surveys and mandatory reporting to the Health Ministry in Nicaragua consistently yielded a proportion of 6% or less of pesticide poisoning cases due to suicide across 1987 and 1991 [Castillo-Martinez and de Vos, 1988; Appel et al., 1991] and in Costa Rica of 10% or less in 1995 and 1996 [Ministerio de Salud, 1996, 1997]. A retrospective record review over a 4-month period in 1996/1997 at the National Health Insurance System in Uruguay found that occupational pesticide poisonings (22%) in public and private facilities exceeded those due to suicide (16%) [Gourmelon, 1999]. While proportions of suicide among pesticide poisoning in some Latin American countries and in some studies [Aguilar, 1988; Espinosa-Gonzalez et al., 1991; Wesseling et al., 1993; Berroterán, 2001; Samayoa et al., 2005] are slightly higher, and appear to approach the percentages reported elsewhere in the world, it is still clear there appears to be a global discrepancy in the epidemiological profile of causative circumstances of pesticide poisoning. For the majority of Latin American country studies listed in Table I, there were more occupational pesticide poisonings than those due to suicide.

Various reviews [Forget, 1993; He et al., 1999] have drawn attention to the divergent patterns of causation reported in different parts of the world, summarized as follows. In most studies in the East and in Africa, suicide appears as the most common single cause of pesticide poisoning, in some cases constituting more than half of the cases. In Latin America, occupational poisonings appear to play a more significant role in the epidemiology of pesticide poisoning, often with little contribution by suicide (see medians for studies from Latin America compared to medians for studies from Asia summarized in Table I). Despite the strong social elements to the causation of suicide, and arguments for the importance of culture in explaining suicide prevalence [Latha et al., 1996; Van der Hoek et al., 1998], no consistent evidence is presented for specific cultural factors as causative. Indeed, wide differences in the prevalence of suicide as a cause of pesticide poisoning are evidenced as much within countries as between countries (Table I).

Where suicide is associated with pesticide poisoning, the agents implicated in suicide are largely OPs [de Alwis and Salgado, 1988; Wesseling et al., 1993; Mbakaya et al., 1994; Gourmelon, 1999; He et al., 1999], carbamates [Saadeh et al., 1996; He et al., 1999], and paraquat [de Alwis and Salgado, 1988; Wesseling et al., 1993, 2001b]. For example, in the Kashmir Valley, suicide attempts accounted for 74% of patients with OP pesticide poisoning [Malik et al., 1998] and 85% of all admissions for OP poisoning admissions in Harare in 1990 [Munyikwa and Levy, cited in Loewenson and Nhachi, 1996]. As would be expected, case-fatality rates (CFRs) from suicidal pesticide poisonings are consistently higher than CFRs from other causes. The ratios between the CFR for suicidal pesticide poisonings to overall CFR for all

TABLE I. Profile of Acute Pesticide Poisoning in Developing Countries

		Percentage distribution of causal circumstances[a]			
Country [reference]	**Setting**	**Occupational**	**Accident**	**Suicide**	**Ratio suicide: occupational**
Africa					
Kenya [Mwanthi and Kimani, 1993]	Review of district hospital records 1987–1990, missing data on cause in 57% cases, no case definition	8		35	>4.4:1
Zimbabwe [Nhachi, 1988]	Teaching hospital records, January 1981 to June 1986, case definition based on clinical diagnosis	15		73	4.9:1
Zimbabwe [Loewenson and Nhachi, 1996]	Admissions to two teaching hospitals, Harare, 1987 and 1988, case definition based on clinical diagnosis	N/S	N/S	85	>5.7:1
South Africa [Department of Health, 1995]	Review of notifications to Ministries of Health	N/A	N/A	22	N/A
South Africa [London et al., 1994]	Review of notification in one province, 1987–1991	11	44	35	3.2:1
Median		**N/C**	**N/C**	**35**	**N/C**
Asia					
India [Gourmelon, 1999]	Record review (both retrospective and prospective data collection at secondary and tertiary health care centers in five provinces 1996/1997 over 8 months	7	18	75	10.7:1
Indonesia [Jeyaratnam et al., 1987]	National hospital record review January–December 1983	2	0	63	31.5:1
Sri Lanka [Jeyaratnam et al., 1987]	National hospital record review January–December 1983	32	29	36	1.1:1
Sri Lanka [de Alwis and Salgado, 1988]	Review of hospital admission 1975–1983	17	8	73	4.3:1
Sri Lanka [Jeyaratnam et al., 1982]	Review of hospital records for 1979, all general hospitals and 5 of 14 base hospitals, no details on criteria for diagnosis	17	8	73	4.3:1
Sri Lanka [Van der Hoek et al., 1998]	Review inpatient records for local hospitals in two districts, 1991–1994	19	13	68	3.4:1
Sri Lanka [Gourmelon, 1999]	Review records at two hospitals over 4 months, 1996/1997	0	7	93	N/C
Malaysia [Lum et al., 1993]	Ministry of health data for 1979–1986	38		49	>1.3:1
Malaysia [Jeyaratnam et al., 1987]	National hospital record review January–December 1983	14	18	68	4.9:1
China [He et al., 1999]	Agricultural workers, not stated in detail	18	N/S	82	4.6:1
Philippines [Castaneda and Rola, 1990, cited in text of Lum et al., 1993]	Department of Health hospital data for 1980–1987 Not stated if only inpatient No details on criteria for diagnosis	14	18	64	4.6:1
Philippines [Castaneda, 1988, cited in text of Lum et al., 1993]	Retrospective hospital record review 1982–1985 Case definition based on clinical diagnosis	18	16	63	3.5:1
Thailand [Jeyaratnam et al., 1987]	National hospital record review January–December 1983	14	9	61	4.4:1
Thailand [Lum et al., 1993]	Three year study by the National Environmental Board, methods not stated	7–26	10	50	1.9–7.1:1

TABLE I. (*Continued*)

Country [reference]	Setting	Percentage distribution of causal circumstances[a]			Ratio suicide: occupational
		Occupational	Accident	Suicide	
Hong Kong [Chan et al., 1996]	Hospital admissions in a large regional hospital, 1988–1991, adjusted for undercount, for missing wards, and for national spread	5	21	74	14.8:1
Median		**14**	**16**	**68**	**4.9:1**
Latin America					
Costa Rica [Ministerio de Salud, 1996]	Notifications to Ministries of Health, 1996	62	9	6	0.1:1
Costa Rica [Ministerio de Salud, 1997]	Notifications to Ministries of Health, 1997	48	9	10	0.2:1
Costa Rica [Proyecto PLAGSALUD, 2002]	Notifications to Ministries of Health, 2001	32	23	20	0.6:1
Central America [Arbeláez and Henao, 2002]	Surveillance data 1999–2000 at the Ministries of Health	39	24	32	0.8:1
Costa Rica [Wesseling et al., 1993]	Hospital records, 1980–1986	50	25	24	0.5:1
	Autopsy records at the Medical Forensic Department, 1980–1986	11	26	62	5.6:1
Costa Rica [Forget, 1993]	(Cites data from PAHO, 1986; not stated what type of data)	68	N/S	6	0.1:1
Panama [Espinosa-Gonzalez et al., 1991]	Hospital records and Social Security records 1981–1990	26	34	32	1.2:1
Nicaragua [Castillo-Martinez and de Vos, 1988]	Hospital registered poisonings in 1987, one region	79	15	6	0.1:1
Nicaragua [Appel et al., 1991]	Notifications to Ministries of Health 1987 for two regions	79–88	9–15	3–6	<0.1:1
Nicaragua [He et al., 1999]	Agricultural workers, not stated in detail	91	N/S	1	<0.1:1
Nicaragua [Berroterán, 2001]	Notifications Ministries of Health 2000 for entire country	33	13	52	1.6:1
Guatemala [Samayoa et al., 2005]	Ministries of Health Reporting 1986–1987	42	36	23	0.5:1
Honduras [Aguilar, 1988]	Ministries of Health Reporting, 1987	31	18	47	1.5:1
Ecuador [Cole et al., 2000]	Intensified passive surveillance, 1991/1992	66	16	18	0.3:1
El Salvador [Department of Epidemiologic Surveillance, Ministry of Health, unpublished]	Ministries of Health reporting for 1998 and 1999	26	31	42	1.6:1
Uruguay [Gourmelon, 1999]	Retrospective record review of National Health Insurance System for public and private facilities around Montevideo over 6 months, 1996/1997	22	60	18	0.8:1
Median		**50**	**25**	**23**	**0.5:1**
Other developing countries					
Jordan [Saadeh et al., 1996]	Teaching Hospital record review, year unstated	10	26	64	6.4:1

N/C, not calculable; N/A, not available; N/S, not supplied.
[a]Undetermined circumstances of poisoning not included—in some cases data do not add to 100% because authors unable to identify circumstances of poisoning.

pesticide poisonings were 1.7 in Sri Lanka [van der Hoek et al., 1998], 2.3 in Costa Rica [Wesseling et al., undated], 5.7 in Ecuador [Cole et al., 2000], 5.8 in Nicaragua [Castillo-Martinez and de Vos, 1988], and 9.2 in Costa Rica [Ministerio de Salud, 1997].

The Importance of Suicide as a Cause of Pesticide Poisoning

The recognition of the importance of suicide due to pesticide poisoning as a public health problem should be placed in a historical context. Levine and Doull [1992] argue that this shift in epidemiological analysis reflected an important new insight.

> ''During the 1970s, the prevailing view in pesticide epidemiology appeared to be that pesticide-related suicide was not an appropriate topic for public health consideration. It was argued that people bent on suicide would do so anyway, and scientists interested in prevention would be better advised to focus their energies elsewhere (Hayes, 1975). Subsequent data, however, suggested that pesticides might be associated with increased rates of suicide within a country (Doon, 1984) and epidemiologists in Papua New Guinea and the South Pacific called attention to the problem of easy access (Banjar and Wasir, 1998, 1990)...''

This observation helped to identify an important hiatus in understanding the problem. But, to some extent, the pendulum appears to have swung in the opposite direction; suicide tends to be automatically viewed as the main problem, and occupational poisoning as the exception. For example, in reviewing pesticide poisoning cases admitted to the two major hospitals in Zimbabwe, Baloyi [1989] argued, without reference to any data, that ''...most accidents caused by pesticides were not occupational, but were due to other causes, e.g., young children ingesting the poison which had obviously not been kept in a safe place, ... eating or drinking from contaminated containers....''

Similarly, Muller et al. [1993], in commenting on poison center data from a large teaching hospital in Cape Town, argued that ''contrary to popular belief, acute OP poisoning as a result of exposure of *farm laborers* during the spraying season *is relatively uncommon*. In fact, surprisingly *few serious acute pesticide poisonings* occur as a result of *exposure during farming activities*'' (italics added).

The view that pesticide poisonings are largely due to suicide is widely held, particularly by clinicians and pathologists. However, as argued below, this view is not necessarily grounded in epidemiological data and may result in inappropriate conclusions.

Underestimation of Non-Suicidal Poisonings With Pesticides

In the developing world, reporting of poisoning due to pesticides may selectively overemphasize poisonings associated with suicide rather than other causes [Murray et al., 2002]. London and Bailie [2001] found that intensification of passive surveillance uncovered under-reporting on the order of 80%, and that under-reporting selectively missed causes other than suicide (and cases among women). Similar attempts to intensify passive reporting in Ecuador showed far higher rates of work-related poisonings than suicides [Cole et al., 2000]. In addition, most studies cited in Table I in Asian and African populations are not based on reporting or surveillance systems but on ad hoc reviews of cases of hospitalized patients, which reflects the lack of established surveillance systems in many developing countries. Even where such systems do exist, great variability in reporting can arise. McConnell et al. [1993] have shown how, within a single country, different surveillance systems can generate rates of poisoning and proportions of poisonings due to suicide that differ by an order of up to tenfold, with hospital based systems tending to overemphasize suicide. Flawed surveillance may, therefore, be the reason why suicide is so common in many reviews of poisoning in developing countries.

There are many reasons why suicide-related poisonings may be more easily reported than other circumstances [London and Bailie, 2001]. Suicidal poisonings tend to be more severe clinically (partly because of the agents used), may be more spectacular in onset, and may be more likely to evoke action from family or friends to seek medical attention and ''hence'' hospitalization. Diagnosis of the poisoning may be easier due to the manner in which exposure occurred. Once hospitalized, the greater severity of the illness may increase the chances of patient transfer to a tertiary service where the chances of notification may be increased. In Thailand, despite an incidence rate as high as 826.8 per 10,000 agricultural workers, only 2.4% of people were hospitalized [Wongphanich et al., 1985]. Evidence from Nicaragua [Keifer et al., 1996a] suggests that the nature of the clinical presentation may well influence the likelihood of reporting of cases of pesticide poisoning. Lastly, there may be systematic misreporting of occupational exposures as suicidal poisonings because of clinician preference. Gourmelon [1999] found that over 10% of cases of occupational pesticide poisoning seen at two Sri Lankan hospitals had been misclassified as either suicide or non-occupational accidents. In reviews of Costa Rican mortuary data, it was found that of 238 deaths classified by forensic services as suicides, 18% were occupational or accidental poisonings and another 29% had insufficient information to define the cause [Wesseling et al., 1993]. Alternatively, misreporting may be specifically linked to reducing financial liability on employers (Dr. Luis Lujan, El Colegio de Michoacan, Mexico, 1998 personal communication). For example, Wesseling et al. [2001a] interpreted a decrease of occupational poisonings among Costa Rican banana workers in 1996 as compared to 1993 as underreporting of milder cases by company doctors to minimize insurance levies. Underreporting may also reflect a gender bias on the part of health professionals due to clinicians' non-recognition of women as farm workers with potential exposure to pesticides [London et al., 2002].

The Relationship Between Suicide and Exposure to Pesticides

Notwithstanding the relationship of suicide and pesticide exposure, what is not always evident is the direction of this association. The commonly articulated explanation for the association between OPs and suicide is the availability of highly toxic pesticides to farm workers and their families [de Alwis and Salgado, 1988; Hettiarachchi and Kodithuwakku, 1989; Diekstra and Gulbinat, 1993; Siwach and Gupta, 1995; Saadeh et al., 1996; Keir and Whiting, 1997; Eddleston et al., 1998; van der Hoek et al., 1998; Gourmelon, 1999; Gunnell and Eddleston, 2003; Eddleston and Phillips, 2004]. Thus, a farm worker with suicidal ideation who has such access to OPs would be more likely to make an attempt (which may be fatal) [Siwach and Gupta, 1995] compared to a situation where they do not have such access [Hettiarachchi and Kodithuwakku, 1989; Flisher, 2000]. In other words, the association of suicides and OPs is based on their availability as a method. If OPs were not available, a proportion of those intending to attempt suicide would not seek another method.

However, a number of mortality studies have begun to explore whether occupational factors (such as farming or specific agricultural exposure to OPs) are risk factors for mortality due to suicide or psychiatric disorders. For example, mortality for psychiatric disorders increased in occupations with pesticide exposure (OR = 1.46; 95% CI 1.33–1.60) in a US death registry study for the years 1988 to 1992 [Van Wijngaarden, 2003] but no data on specific outcomes, such as suicide or depression, were given in this study. A mortality study of migrant farm workers in the US [Colt et al., 2001] found significantly increased age-adjusted proportionate mortality from mental and psychoneurotic disorders among white/Hispanic (Proportional mortality ratio (PMR) = 146; 95% CI 129–165) and "non-white" (PMR = 127; 95% CI 109–147) men, although PMRs directly due to suicide were reduced (PMR = 79; 95% CI 71–87, and PMR = 69; 95% CI 51–92, respectively). The authors hypothesized that cultural factors may lead to underreporting of suicide as the cause of death. In contrast, proportionate mortality between 1984 and 1993 due to suicide was found to be significantly increased in white male crop and livestock farmers compared to the general population of 26 US states (PMR's varied from 110 to 122 depending on age stratum), and no evidence of increased mortality due to mental disorders was present [Lee et al., 2002]. These conflicting findings may indicate different morbidity patterns for farm workers and self-employed farmers, although proportionate mortality studies are difficult to interpret because of the effect of competing causes of death.

Nonetheless, the literature confirms that suicide rates among farmers (independent of the method used) are elevated [Boxer et al., 1995; Gregoire, 2002] particularly in developing countries with heavy reliance on agriculture [Keir and Whiting, 1997; Khan, 2002; Eddleston and Phillips, 2004]. The question is whether pesticide exposure, specifically to OPs, plays a role in elevating risk for suicide.

In a cohort study of Canadian farmers, cases of completed suicide over a 17-year period were matched to controls, and compared with regard to pesticide exposures reported to an agricultural census at the start of the study period [Pickett et al., 1998]. The study found no associations between suicide and acres sprayed with insecticides, but did suggest an increase in risk associated with herbicide and insecticide spraying among a moderately exposed subgroup compared to non-exposed farm operators (OR = 1.71; 95% CI = 1.08–2.71). No data specific to OP exposure was available in this study. On the other hand, mortality studies among Italian licensed pesticide users failed to show any increased risks for suicide [Torchio et al., 1994; Sperati et al., 1999].

OPs as Neurotoxins: Depression, Mood, and Psychiatric Disorders

Mortality studies are usually based on retrospective data of variable quality, resulting in the possibility of misclassification for OP exposure. Alternative sources of data from studies exploring affective and other psychiatric disorders may, therefore, be useful in identifying the causative factors elevating suicide risk among farmers. Given that OPs are known to affect the CNS [De Bleecker et al., 1993; Maroni and Fait, 1993; Bolla and Roca, 1994; Singh and Sharma, 2000; Colosio et al., 2003; Delgado et al., 2004], it is not implausible that OP exposure may have psychiatric or affective consequences.

Animal Data and Neuropharmacology: Biological Plausibility?

A number of animal studies have identified the impact of OP exposure on neurotransmitter and neuroendocrine function in the brain, particularly the link with serotonin levels [Maslinska et al., 1981; Rajendra et al., 1986; Singh and Drewes, 1987; el-Etri et al., 1992; Raines et al., 2001; Aldridge et al., 2003]. Given an increasing number of studies exploring the association between depression, suicide, and lowered serotonin levels in the central nervous system in humans [Oquendo and Mann, 2000; van Heeringen, 2001], and animal data showing impacts on serotonin levels at concentrations below that needed to inhibit cholinesterase [Aldridge et al., 2003], there appears to be some plausibility for the hypothesis that OP effects on mood may be mediated by non-cholinesterase mechanisms involving serotonin. Impulsivity, a major factor reported to be associated with suicidal acts, has been shown to be associated with lower serotonin in depressed subjects [Oquendo and Mann, 2000].

Evidence From Human Studies

There is consistent evidence from several clinical studies and case series that chronic exposure to OP pesticides may be associated with affective disorders, especially depression [Rowntree et al., 1950; Gershon and Shaw, 1961; Dille and Smith, 1964; Joubert and Joubert, 1988; Bradwell, 1994; Davies et al., 2000], anxiety [Dille and Smith, 1964; Namba et al., 1971], and unprovoked aggressive behavior [Devinsky et al., 1992]. Notwithstanding their limited epidemiological validity, there are also several ecological studies supporting a potential link between OP exposure and suicide [Crombie, 1991; Kelly et al., 1995; Parrón et al., 1996].

Epidemiological studies of CNS effects following acute poisoning have reported a range of acute neuropsychiatric symptoms [Jamal, 1997] such as psychotic episodes [Churkin and Sadovnikova, 1981; Hall et al., 1981; Merrill and Mihm, 1982; Parker and Brown, 1989] and extrapyramidal manifestations [Joubert and Joubert, 1988; Senanayake and Sanmuganathan, 1995]. Moreover, a variety of chronic neuropsychological effects have been reported as following acute poisoning. These have included impaired cognitive functioning and motor skills, accompanied by higher scores for defensiveness, paranoia, and social introversion [Savage et al., 1988]; poorer performance on sustained visual attention and mood scales, specifically higher scores on Tension and Confusion scales of Profile of Mood States (POMS) questionnaire [Steenland et al., 1994]; poorer auditory attention, visual memory, visuomotor functions, and increased neurobehavioral symptoms, specifically higher somatization scores on the Brief Symptom Inventory [Rosenstock et al., 1991]; impaired psychomotor and visuomotor skills, language function, neuropsychiatric symptoms and affect [Wesseling et al., 2002]; Mild Psychiatric Disorder [Faria et al., 1999] and increased neurobehavioral symptom scores [London et al., 1998]. Notably, the study of OP poisoning cases in Nicaragua [Rosenstock et al., 1991] showed no differences in BSI scores for depressive symptoms, a result the authors used to exclude confounding by post-poisoning depression. However, Savage et al. [1998] noted that family members of OP poisoned subjects reported depression, irritability, and social withdrawal in the index cases more commonly than control families, indicating collateral evidence for impairment of everyday functioning among OP poisoning survivors. More recently, a cross-sectional study of 761 Colorado farmers found that self-reported pesticide poisoning was associated with more than five times increased risk for depression based on the Centre for Epidemiologic Studies-Depression Scale [Stallones and Beseler, 2002].

In contrast to the situation for acute intoxication, consensus is still awaited regarding the CNS effects of low-dose ongoing OP exposure, in the absence of acute poisoning. The few studies conducted to date, while characterized by methodological shortcomings, have suggested subtle neurobehavioral impairments but have generally yielded contradictory or equivocal results [Colosio et al., 2003]. Levin et al. [1976] were among the first to draw attention to the possibility of psychiatric disorders being linked to low level exposure to OPs when they found 13 commercial pesticide sprayers to have higher anxiety scores on a standardized psychological test battery than 24 non-exposed controls, but no differences on the Beck Depression Inventory (BDI). Richter et al. [1992] found some evidence of increased symptoms, including depression, and poorer performance on standardized neurobehavioral tests among kibbutz workers and residents with OP exposure, but the study was complicated by potential selection bias and other methodological weaknesses. A study of 57 exposed male fruit farmers and 42 age-matched male controls found evidence of impaired reaction time but no differences on tests of concentration, visuomotor skills, memory, expressive language, or mood [Fiedler et al., 1997]. Exposed greenhouse workers in Poland reported higher levels of anxiety, depression and fatigue-inertia on the Profile of Moods States (POMS) questionnaire than unexposed controls, but showed no change in scores after seasonal exposure [Bazylewicz-Walckzak et al., 1999]. Other studies have been negative for CNS consequences of long-term exposure [e.g., Rodnitzy et al., 1975; London et al., 1997] even in the presence of vibration threshold impairment [Stokes et al., 1995] or have suggested that OP exposure below levels associated with cholinesterase depression are not associated with any neurobehavioral impairments [Ames et al., 1995].

Symptoms in Neurobehavioral Studies

Where studies on long-term effects of exposure to OPs have demonstrated positive associations, these have been strongest for adverse symptom outcomes. South African fruit farm workers reporting a past poisoning with pesticides requiring medical care, were four times more likely to report high levels of neurological and neuropsychiatric symptoms than non-poisoned colleagues [London et al., 1997]. Banana plantation workers in Costa Rica previously poisoned with cholinesterase-inhibiting pesticides scored almost double their non-poisoned colleagues on a standardized neuropsychiatric symptom inventory [Wesseling et al., 1997]. In particular, the score for the depression symptoms cluster was significantly higher for workers reporting previous poisoning with OPs compared to non-poisoned controls (OR = 2.9; 95% CI 1.3–6.6). A small study of 21 migrant workers who survived acute poisoning from different pesticides including OPs were found to have increased depression-related symptoms compared to 11 controls matched for age, sex, education, socioeconomic status, and ethnicity [Reidy et al., 1992]. A Nicaraguan study of patients hospitalized for occupational OP poisonings did not find increased symptoms compared to non-poisoned controls at discharge nor 7 weeks later, but large excesses were present 2 years post-poisoning, more prominently among severely poisoned workers [Delgado et al., 2004].

Even with respect to long-term exposures without acute poisoning, there is some evidence that symptoms may be the strongest indicators of subtle neurobehavioral impacts. For example, 191 current and former termiticide applicators with an average of 2.4 years exposure to the OP chlorpyrifos reported significantly more memory problems and symptoms related to emotional state and fatigue compared to 189 nonexposed controls [Steenland et al., 2000]. The strength and consistency of the association with these symptoms far exceeded the few effects found for other measures of neurobehavioral performance and sub-group analyses showed differences between exposed applicators and controls for the depression scale on the POMS. Keifer et al. [1996b] reported higher levels of symptoms, including those related to depression, among rural Nicaraguans living near cotton fields sprayed with a range of pesticides including OPs. Greater vulnerability to psychiatric disorders as measured by the General Health Questionnaire (GHQ) [Goldberg and Hiller, 1979] was found in OP-exposed sheep farmers in the UK compared to quarry worker controls [Stephens et al., 1995] and in Egyptian factory workers formulating OPs, who also reported higher frequencies of psychiatric disorders (as defined in the DSM III R), particularly depressive neurosis and reactive depression [Amr et al., 1997].

The data, therefore, suggest a possible etiological pathway in which exposure to OPs acts in a biological/toxicological sense as a cause of suicide, in addition to being a potential agent of suicide (see Fig. 1).

This biological causal pathway could be mediated either through depressive CNS effects, or through an effect on impulsivity, or perhaps both (Fig. 2). In all of these models, OPs may reappear later in the pathway as agents for the suicide, although other pesticides or methods may also be used.

If OPs are in some way causally related to suicide, this effect may not be mediated through cholinesterase inhibition. Indeed, much of evidence suggesting CNS effects of low level chronic exposure implies that other, more sensitive, brain proteins are likely targets [Singh and Drewes, 1987]. These effects would be expected to show very different structure–activity relationships to acute toxicity mediated by acetylcholinesterase [Ray and Richards, 2001]. For example, the developmental toxicity of chlorpyrifos appears to be mediated through non-cholinergic mechanisms at specific developmental windows involving serotonergic systems [Aldridge et al., 2003]. By analogy, Organophosphate (OP)-Induced Delayed Neuropathy has been shown to be mediated by an esterase entirely unrelated to the acetylcholinesterase

- OP´s are known neurotoxins, both acute and chronic
- OP´s are able to cause CNS dysfunction
- In particular, extensive evidence confirms that acute poisonings can result in a range of neurological and neuropsychiatric disturbances, that may be compatible with affective disorders
- Evidence from long-term low dose exposure studies amongst humans are equivocal, but some evidence for an effect on psychiatric state and affect have been recorded
- Where neurobehavioural effects have been seen in long-term exposure studies with OP´s, the most sensitive effects appear to be symptom outcomes, more closely linked to affective disorders.
- Clinical case series provide support for a causal relationship between chronic exposure to OP´s and affective disorder, especially depression.
- Three ecological studies in the literature identify an association of OP use and suicide.
- Animal data show a link with organophosphate exposure and serotonin levels and function in the brain, supporting a possible link between depression and OP exposure.

FIGURE 1. Conclusions from the literature supporting a possible causal link between organophosphate (OP) exposure and depression.

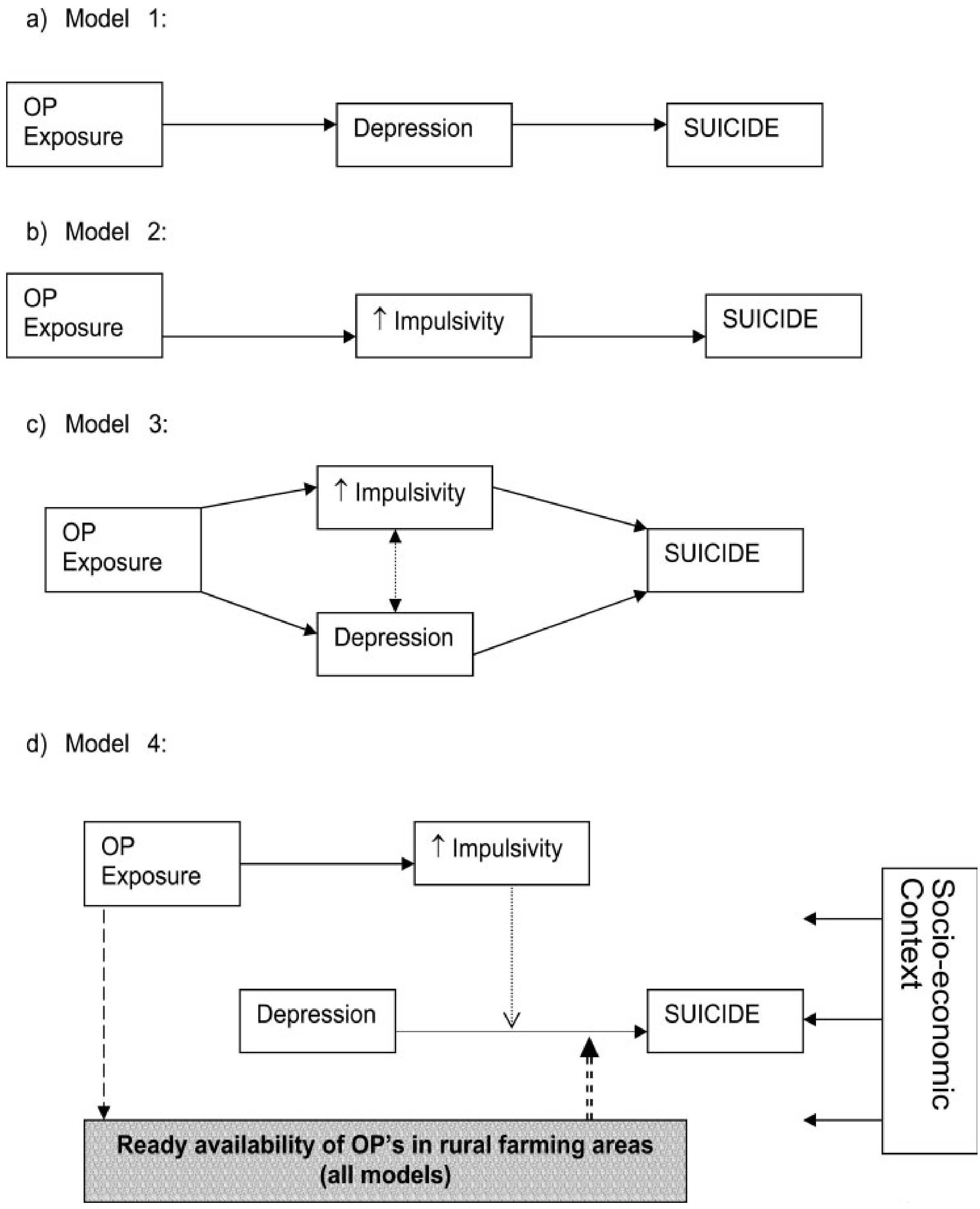

FIGURE 2. Potential causal models: OP exposure and suicide.

associated with acute OP neurotoxicity [Maroni and Fait, 1993]. Thus, one of the implications of distinct OPs having different neurotoxic mechanisms and effects is that epidemiological studies that base exposure on class OP effects may misclassify critical exposures, and produce variable results or false negatives [Ray and Richards, 2001].

Policy Implications

Farmer indebtedness, rooted in unfair economic systems in developing countries, is an increasingly important phenomenon driving up rates of suicide among farmers and farm workers [Dinham, 1999; Shiva et al., 2002; Christian

Aid, 2002]. Little is known about the possible interactions of these social factors with toxic exposures such as OPs. Given the dire situations of poverty and deprivation faced by the majority of rural people in developing countries [Dinham and Malik, 2003], consequences of pesticide exposures such as suicide could easily be viewed as part of a spectrum of human rights violations experienced by vulnerable communities [London, 2003].

Responses to the association between suicide and OP exposure may exacerbate these injustices, particularly given a focus on controlling individual risk factors evident in occupational health services generally [World Health Organization, 1985], in suicide prevention programs specifically [Onyon and Volans, 1987; Bowles, 1995; Keir and Whiting, 1997; Eddleston, 2000; Eddleston and Phillips, 2004; Knox et al., 2004] and in industry's ''Safe Use'' strategies for pesticides [Ellis, 1998; Murray and Taylor, 2000, 2001]. As applied to the prevention of pesticide-related suicide, the latter would involve measures such as educating individuals, raising awareness, adding emetics, or foul-smelling agents to discourage ingestion, or at least preventing access for suicidal persons intent on using pesticides to kill themselves by improving industrial housekeeping practices. Not surprisingly, research focused on individual risk factors for pesticide-related suicide has proven attractive to industry. A Befrienders International study of suicide-related pesticides funded by Zeneca Agro-Chemicals [Keir and Whiting, 1997] dedicated only one paragraph and one non-indexed reference out of 60 pages to the possible causal role of OPs and, concluded that the problem was one of access, requiring secure storage, better statistics, restraint by the media in reporting suicide, and ''. . .prevention initiatives . . . aimed at the establishment of trained listeners to provide emotional support to those in distress.''

Under circumstances where individuals are held fundamentally responsible for the problem, liability does not accrue to those who manufacture, distribute or regulate these hazardous products. Comprehensive approaches to the prevention of suicide caused by OP exposure would go beyond individual risk factors, for example, through legislation on availability coupled with changes in farming practice [Konradsen et al., 2003].

A feature of these responses is that the social or political context in which, suicides and pesticides are linked is not challenged. The idea of a ''pesticide culture'' refers to the widespread social acceptance of pesticide usage as a norm, and the belief that pesticides usage is both safe and necessary, and is manifested in the manner in which pesticides are marketed, advertised, regulated and researched [Rother and London, 1998]. For example, the conclusions of the Befrienders International Study [Keir and Whiting, 1997] simultaneously acknowledge as given the notion that pesticides are ''an essential component of the agricultural economy'' while calling for action to reduce the frequent use of pesticides as a means of suicide. In this perspective, hazards to human health and the environment from pesticides are viewed as the exception, adequately controlled by regulation, education, or other measures adopted by private and public sectors [Rother and London, 1998]. The ''pesticide culture'' thereby contributes to the individualization of risk, by identifying suicide with errant personal behavior, attributes or psychiatric disease, while maintaining that proper use poses no threat to ''normal'' persons. However, as shown in Sri Lanka, programs that promote the safe use of pesticides through education and training of farmers will be ineffective because, in many cases, knowledge is already high [Van der Hoek et al., 1998].

The data presented in this review, therefore, challenge the notion of suicide as a non-occupational problem by identifying a potential causal mechanism by which exposure to OPs may be contributory to suicide through biological pathways independent of issues of access to OPs as the agent for a suicidal act. If OPs are causal in the pathway to suicide, whether it is a suicidal act using a pesticide or another agent, this would represent a significant contributor to the burden of disease suffered by those populations with limited resources to deal with the problem. Rather than shifting responsibility for the problem onto individuals through implementing controls based on personal responsibility, accountability for the problem would have to be appropriately apportioned. The policy consequences of such a different conceptualization are wide-ranging, implying more rigorous risk assessment, stricter regulatory decisions and upstream control measures, such as greater emphasis on pesticide use reduction policies.

CONCLUSION

There are significant and consistent differences in the epidemiological patterns of the circumstances of pesticide poisoning across the globe, and these differences do not seem to be adequately explained by cultural differences. Suicide may be overreported as a relative cause of morbidity and mortality in developing countries, particularly in relation to occupational causes, for various reasons. While the focus on suicide has provided an important insight into the public health problems facing pesticide-exposed populations, it has also put potential obstacles in the way of conceptualizing control measures, particularly in relation to industry responsibility. Our review presents evidence that pesticide exposure, in particular to OPs, may have a causal relationship to suicide.

Rigorous epidemiological studies with stronger study designs are, therefore, needed to evaluate the potential relationship between exposure to OPs and suicide. Key to these studies would be careful exposure characterization that has high specificity for OP exposure, which readily distinguishes short- and long-term exposure, and that uses outcome measures validated for local populations in different cultural contexts. Collaborative research is currently underway between the researchers in South Africa, Holland, Tanzania, Canada, and Costa Rica to explore the hypothesis that exposure to OP insecticides may contribute causally to the problem of suicide among rural farming populations using pesticides and to identify strategies to address the problem [Major and London, 2003]. Data from such studies may contribute not only to expanding scientific knowledge on the potential hazards of pesticides, but also contribute directly to alleviate part of the disease burden borne by the most marginal populations in developing countries.

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