wetenschapswinkel

a pilot study

Suicide and depression resulting from exposure to pesticides among tobacco farmers in Paraná, Brazil

Natascha M. Smits

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Wageningen, January 2000

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Suicide and depression resulting from exposure to pesticides among tobacco farmers in Paraná, Brazil

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PREFACE

Representatives of the Agro-Social Desk of "Mission and World Service of the Reformed Churches in the Netherlands" (now called Global Ministries) were informed by a local Brazilian project leader about an excessive rate of suicide among tobacco farmers in Paraná, Brazil. It was conjectured that exposure to pesticides in the tobacco farming industries in Brazil may lead to a psychological depression, resulting in an excessive rate of suicide. Therefore, the Agro-Social Desk asked the Science Shop of Liaison Office of Wageningen University to organize a study to assess the possibility of a causal relationship between the use of certain pesticides in tobacco cultivation in Brazil and increased levels of depression and suicide. The findings of this study are described in the present report.
The Agro-Social Desk will use this generated information to improve the situation of the tobacco farmers by drawing attention to their problems and by giving information and advice.
Natascha Smits of the Environmental and Occupational Health Group of Wageningen University undertook the study; she was supported by Mieke Lumens. Natascha Smits gathered all of the relevant information with great enthousiasm and dedication. She had contact with experts in Brazil, Canada and the Netherlands and is especially grateful to Bram Brouwer, Virginia Etges, Grietje ten Hoeve, John Hollands, Nico Mentink, Donna Mergler, Petra Naber, Cristina Perez, Acir Rickli, Silvana Rubano and Annet van Zweep for their useful contributions.
In addition to the contribution made by Mieke Lumens (Environmental and Occupational Health Group of Wageningen University) this study was also supported by Antoon de Groot and Geert Klaassen (Agro Social Desk of "Mission and World Service of the Reformed Churches in the Netherlands") and by Jantsje van Loon (Liaison Office of Wageningen University).
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SUMMARY

Producing 7% of the world's tobacco, Brazil ranks among the top five of tobacco producing countries in the world. Between 1950 and 1980 in particular the tobacco production rose tremendously. Production kept rising until 1997, with a total production of more than 600,000 tons.
Ninety percent of the land used for tobacco cultivation is situated in the south of Brazil, in the states Paraná, Santa Catharina and Rio Grande do Sul. Normal amounts of pesticide application approach 30 kilograms per hectare per year. In dry years these levels increase and can even reach as much as 100 kilograms (Hickey, 1998). Many pesticides used in tobacco cultivation are highly toxic and their use is increasing.

Most tobacco is cultivated on small independent family farms; because tobacco is labor-intensive all family members, including small children, work in the field. The 'Association of Brazilian Tobacco Growers' estimates that there are 150,000 tobacco farms with a mean area of 2.3 ha of tobacco crop. An estimated 750,000, men, women and children work on these farms.

In the past few years, scientists, non-governmental organizations and other action groups in Brazil have drawn attention to the situation of the tobacco farmers in the southern states. In addition to studies on the farmers' poor social-economical situation, their dependency on the tobacco industry, pesticide intoxications, and potential forestry problems, attention also has been given to the elevated levels of depression and suicide among tobacco farmers.

Field workers from the 'Global Ministries' in the Netherlands also became aware of the high rates of depression and suicides among tobacco farmers in Paraná. They launched the pilot study 'Depression and suicide resulting from exposure to pesticides among tobacco farmers in Paraná, Brazil'. This four-month project studied *the possibility of a causal relationship between the use of certain pesticides in tobacco cultivation in Brazil and elevated levels of depression and suicide.*

Elevated levels of depression and suicide

Mean suicide rates among farmers in the tobacco states Rio Grande do Sul and Paraná were 8.09 and 5.25 per 100,000 inhabitants in 1989. The average suicide rates in Brazil as a whole are 3.20. High suicide rates among farmers are common in many countries.
In general, more than half of the suicide attempts is due to depression. Many social and psychiatric factors can play a role in disposing people to commit suicide. Poverty, instability, constant stress and the absence of social controls can lead to suicide attempts. In addition marital problems, psychiatric and physical illnesses, and alcohol and drug abuse dispose people to commit suicide. There are clear correlations between unemployment, divorce and crime rates. The easy availability of toxic substances and the publicity given to cases of suicide also play a role in high suicide rates.

Both major depression and extremely intensive dysthmia (a milder form of depression) can lead to suicide attempts. There are several psychological and physiological theories on the development of depression. There is a growing awareness that chemicals also can induce a depressive mood. Scientific research, however, is difficult and has to take many factors into account. Chemicals that showed a positive correlation with depression in several scientific studies are *carbon disulfide, organic solvent mixtures, lead, mercury, and organophosphate pesticides.*

Both suicide and depression are complex items and it is often impossible to point out one specific cause. Furthermore, research on the neurotoxicological origin of high suicide rates is complex and has to deal with many confounding factors. This is especially the case in this study. An attempt has been made to take into account as many factors as possible, but conclusions have to be drawn carefully and have to be placed in a broad perspective.

Pesticides as a cause of depression

Affective disorders (or mood disorders) are believed to result from a complex balance between adrenergic and cholinergic factors in those areas of the brain which regulate affect. These factors are the neurotransmitter acetylcholine and the mono-amines dopamine, norepinephrine and serotonin.
Two groups of pesticides, the organophosphates and carbamates, are able to cause an increase in the amount of acetylcholine in the brain. Other groups of pesticides might also be able to influence the central nervous system (and possibly depression), but this assumption is based on laboratory findings or toxicological theories. The most important among these groups of pesticides are organochlorines, pyrethroid esters, ethylene dithiocarbamates, methyl bromide, organomercurial compounds, fluoro-acetate and acetamide.

Approximately fifteen years after the introduction of organophosphate pesticides, the first cases of pesticide-induced depression were reported. Only since the Eighties have there been epidemiological studies which include the relationship between exposure to pesticides and depression or suicide.
Three kinds of epidemiological studies can be distinguished: 1) studies on chronic exposure to pesticides and suicide; 2) studies on chronic pesticide exposure and depression; and 3) studies on acute exposure to pesticides and depression.

These studies involve many different exposure groups, such as sprayers in malaria control programs, farmers in general, banana workers or forestry workers. The studies deal with such problems as assessing the exposure rates and the effect levels. Nevertheless, these investigations raise the suspicion that in reality there may be a causal relation between acute high levels of exposure to pesticides and depressive disorder, mainly in cases of organophosphate poisoning and potentially in cases of organochlorine and carbamate poisoning. The epidemiological studies do not show enough evidence for a causal relationship between depression and chronic low levels of exposure. But since there is no hard evidence to the contrary further epidemiological research in this field should be done.

Risk assessment

Unintentional pesticide poisonings, both occupational and non-occupational, affect many tobacco farmers in Paraná. Among the pesticides frequently causing these incidents of poisoning are the group of organophosphates. Toxicological and epidemiological studies point out that organophosphates may very well have a causal relationship with depressive disorders. Therefore, cases of organophosphate poisoning might be an important risk group.

Because no hard evidence or threshold limits exist for pesticides with regard to depressive disorders, and because of the absence of information on exposure to pesticides levels during tobacco farming in Paraná, no proper risk assessment for chronic low exposure is possible. However, of the 27 most important pesticides used in tobacco cultivation, almost half is likely to have a causal relationship with depressive disorders.
The one study available on exposure to pesticides among tobacco farmers was done in Kentucky. Exposure levels in this study do not exceed existing safety limits, but caution was advised. It is known that Brazilian application techniques and methods of working differ greatly from those in Kentucky. Therefore, it is not possible to simply extrapolate these data to the Brazilian situation.

In addition to the occupational exposure to pesticides, the domestic use of pesticides, other farming activities, ambient exposure and residues in food are all likely to contribute to the chronic exposure to pesticides among tobacco farmers in Paraná and to an increase in the pesticide burden. Some of these exposures are either indirectly related to tobacco farming and other agricultural activities or to the easy availability of pesticides.

Besides to the risk of exposure to pesticides, Brazilian tobacco farmers are also subject to other risk factors for depression and suicide . The most important factors are financial problems, dependency on other companies, the easy availability of toxic substances and the publicity given to cases of suicide. However, it is not possible to quantify this information or to assess the actual impact.

Conclusion

The aim of this pilot study was to assess the possibility of a causal relationship between the use of certain pesticides in tobacco cultivation in Brazil and elevated levels of depression and suicide. The results of this study are not based on either field observations or measurements; in fact many assumptions have had to be made. But the available information *suggests that such a causal relationship, although not proven, may indeed exist.*

Recommendations

In view of the scope and conclusion of this study, it is not possible to give specific practical recommendations. Further research is needed to get more specific answers to fulfill the objectives of this study. But, if a causal relation between exposure to certain pesticides and elevated levels of depression and suicides among tobacco

farmers does exist in Paraná, the exposure levels should be minimized. This causal relationship, however, has not yet been proven. Therefore, it is important not to ignore other factors influencing the occurrence of depression and suicide, factors such as dependencyon other companies, financial problems, the easy availability of toxic chemicals and publicity given to acts of suicide.

Recommendations on minimizing exposure aim at 1) minimizing the occupational exposure of tobacco farmers to pesticides which are suspected of causing depression and suicide; 2) decreasing the number of unintended poisonings with these pesticides; and 3) minimizing non-occupational exposure to these pesticides by environmental contamination and pesticide residues on food.
Further studies should be done on the following pesticides used in tobacco cultivation:
Sevin 7,5 and Carvin (carbaryl), Acefate Fersol 750 PS (acephate), Orthene 750 BR (acephate), Doser, Confidor 700 GRDA (imidachlorprid), Lorsban 480 BR (chlorpyrifos), Solvirex (disulfoton), Furadan (carbofuran), Temik (aldicarb), Brometo de Metila (methyl bromide), Dithane PM (maneb), Manzate 800 PM (mancozeb), and Formicida Mirex (sulfluramide).

General advice can be given by following the general FAO Guidelines on 'Good Practice for Ground and Aerial Application of Pesticides' (1988) and the FAO Guidelines for 'Personal Protection when Working with Pesticides in Tropical Climates' (1990a).
At the level of the individual farmer, the proper use of personal safety equipment and the improvement of work practices and equipment can be achieved by for instance training and education. Special attention should be paid to exposure to pesticides during the mixing and loading of pesticides, their safe storage and the proper disposal of empty pesticide containers.
A system of Integrated Pest Management should also be implemented. Furthermore, at a higher level, improved legislation and maintenance of regulations should play an important role in minimizing exposure to pesticides at work, at home and on food residues.

For more fundamental conclusions specifically related to the practical situation of tobacco farmers in Paraná, Brazil, the following scientific studies are recommended:
- toxicological research to gain more knowledge on the relation between pesticides and depression and suicide, including toxicological mechanism, threshold levels and effect modificators;
- epidemiological studies to gain insight into the rates of depression and suicides among tobacco farmers in the state of Paraná and other tobacco states in Brazil compared to other farmers and the mean population;
- research to gain insight into other risk factors on depression and suicide, such as social-economical, psychological and chemical factors;
- epidemiological research on exposure to pesticides and depression and suicides among tobacco farmers in Brazil to gain more insight into the actual causal relationship. This could be achieved, for instance, by a cohort study including field measurements to determine the occupational and non-occupational exposure of tobacco farmers to pesticides, which are able to cause depressive disorders, measurements of both acute high levels and chronic low levels of exposure, and

measurements of affect from for instance neuropsychological tests. Another epidemiological study could involve a case-control study, in which the exposure to pesticides among a group of depressed individuals is assessed compared to the exposure among a group of non-depressed people;
- research to formulate control measures to lessen the risk faced by tobacco farmers in Paraná at the individual, industrial and state level.

In November 1999 a comprehensive epidemiological study on health, environment, and socio-economical problems among tobacco farmers will start in Rio Grande do Sul. In line with the objectives of the Global Ministries in the Netherlands, it is advisable to pay attention to the results of this research. Final results are expected in August 2001.

Chapter 1 INTRODUCTION AND GOALS

In 1996 in Venancio Aires, a municipality in the state of Rio Grande do Sul, Brazil, suicide rates reached 21.8 suicides per 100,000 inhabitants. This is nearly seven times the average Brazilian suicide rate of 3.2 per 100,000 (Hickey, 1998). Other municipalities in the region showed similar rates (PANNA, 1997). Tobacco production is the chief economic activity in this region. Researchers of the Federal University of Rio Grande Do Sul found that 66% of the dead had worked on tobacco farms, and that April, October, November and December were the months with the highest levels of suicides. These months coincide with the seeding and harvesting of tobacco plants, periods in which organophosphate pesticides (i.e. metamidofos) are used intensively (Falk, 1996).
Mean suicide rates in the tobacco states Rio Grande do Sul and Paraná were 8.09 and 5.25 per 100,000 inhabitants in 1989 (Falk, 1996). Researchers and tobacco farmers voiced the suspicion that the exposure to pesticides in tobacco farming in Brazil leads to a high prevalence of psychological depression, resulting in excessive rates of suicide.

Field workers of 'Mission and World Services of the Reformed Churches in the Netherlands' (now called 'Global Ministries') also became aware of the problem of high rates of depression and suicides among tobacco farmers in Paraná. They launched the pilot study 'Depression and suicide due to exposure to pesticides among tobacco farmers in Paraná, Brazil'. This four-month project studied *the possibility of a causal relationship between the use of certain pesticides in tobacco cultivation in Brazil and elevated levels of depression and suicide*.

The general objective of the study was divided into the following specific objectives:
- to determine if the use of certain types of pesticides could be the cause of a relatively high rate of depression and suicide among those applying pesticides to crops;
- to evaluate the toxicological possibilities of pesticides causing depression;
- to evaluate epidemiological studies on the relation between exposure to pesticides and depression and suicide;
- to determine the types of pesticides used in tobacco cultivation in Brazil;
- to get an impression of the occupational exposure of tobacco farmers by assessing techniques of application, amounts of pesticides used, and the use and effectiveness of personal protection;
- to evaluate other factors that may lead to high rates of depression and suicide among tobacco farmers in Brazil.

The sources of information are the following:
- official literature from the following data bases: CAB Abstracts (1972-April 1999), AGRICOLA (1970-June 1999), AGRIS (1975-May 1999), Current Contents (R) 7 editions (1996-July 2nd 1999) and MEDLINE (R) advanced (1966-July 1999) and references available in literature;
- documents from La Red de Acción en Plaguicidas y sus Alternativas para América Latína (RAP-AL) and The Pesticide Action Network North America Regional Centre (PANNA);
- documentation and information from the University of Santa Cruz do Sul (UNISC),

the Brazilian National Cancer Institute (INCA) and its National Coordination of Tobacco Control and the Surveillance and Prevention of Cancer;
- oral and written conversations with experts in the field of psychology and toxicology;
- information available on the Internet;
- documentation from the Global Ministries in the Netherlands.

This document includes the scientific report. For field research, a more practical report was written in Portuguese.

Chapter 2 TOBACCO CULTIVATION IN BRAZIL

Producing 7% (dry weight) of the world tobacco production, Brazil ranks among the top five of tobacco producing countries in the world (Hickey, 1998). Brazil has a long history of tobacco cultivation and domestic use for rituals and ceremonies. Colonialists used tobacco as a stimulant and introduced the crop and its product to Europe and other parts of the world (Goodman, 1993). From the beginning, Brazil has been a very important supplier of tobacco, and production levels have continued to grow. Between 1950 and 1980 especially the tobacco production rose tremendously. The yield multiplied four times to more than 400,000 tons per year (Nardi, 1985). The production kept rising until 1997, with more than 600,000 tons per year. (FAOSTAT, 1999). In 1997 and 1998 however El Niño brought storms and heavy rainfall, resulting in lower yields in 1998 (Cordeiro, 1998b; Osava, 1998).
In 1997, tobacco exports represented one-third of Brazil's agricultural income, only surpassed by soybeans and coffee. Almost 300,000 tons of tobacco were exported, worth almost 1 billion USD. The Brazilian government offers multinational tobacco companies corporate subsidies such as low taxes and cheap credit. This makes the tobacco industry a very profitable business.

Ninety percent of the land used for tobacco cultivation is situated in the south of Brazil, in the states Paraná, Santa Catharina and Rio Grande do Sul. In the northern state of Bahia, tobacco is cultivated ecologically (Armani, 1998). In the tobacco cultivation in the south, however, pesticide use is intensive. Normal application rates approach 30 kilograms of pesticides per hectare per year. In dry years these levels increase and can even reach as much as 100 kilograms (Hickey, 1998). Many pesticides used in the tobacco cultivation are highly toxic and their use is increasing (Cordeiro, 1998a). Most pesticides used in the field are produced by Bayer.

Most tobacco is cultivated on small independent family farms, and because tobacco is labor-intensive, all family members, including small children, work in the field. The 'Association of Brazilian Tobacco Growers' estimates that there are 150.000 farms, with a mean area of 2.3 ha of tobacco crop (AFUBRA, 1997; Cordeiro, 1998a). An estimated 750,000 men, women and children work on these farms (Andrei, 1996).

Nowadays powerful cigarette industries and leaf exporters are the most important buyers of tobacco leaves. Souza Cruz (owned by British-American Tobacco) and Philip Morris have large interests in Southern Brazil. Most farms have contracts with these companies. They determine the precise amount of tobacco to be planted and how much and what kinds of pesticides and fertilizers will be used. They frequently visit the farmers to check all phases of the production process, such as sowing, curing and grading, and the application of fertilizers and pesticides. Then they charge the farmers for their 'technical assistance'.
The tobacco companies are also the place where a farmer can get a loan or credit to purchase sowing seed, pesticides, and growth regulators and to construct curing sheds. At the end of the season, farmers are paid according to the quality of their tobacco. The value of the crop is determined at a large distance from the farms, by the company itself. The farmer must pay for any damages during transport. Expenditures include the costs of pesticides and fertilizers. In a bad year purchases decline, so debts have to be paid off with yields from other crops, such as maize,

beans or onions (Goodman, 1993; Hickey, 1998). However, in a good year, tobacco is a favorite crop, with an gross income of approximately 3,000 USD/ha. Despite all the problems, farmers feel that the tobacco companies offer security (Cordeiro, 1998).

During many stages of tobacco cultivation the farm workers can be exposed to pesticides, growth regulators and nicotine. Pesticide poisonings are widespread among tobacco farmers and community members (Hickey, 1998). Green Tobacco Sickness (GTS), an acute illness caused by exposure to nicotine from wet tobacco leaves and resulting in symptoms such as vomiting, giddiness and headache, is also reported to be a major occupational health problem (Ghosh, 1979; Ghosh, 1985).

Tobacco cultivation not only cause health problems, but also threat the environment. Questions have been raised, for instance, about pesticides leaking into ground and surface waters (Inoue, 1993; Thrupp, 1994) and deforestation (ITGA, 1998). Flue cured tobacco (a variety that is dried in a heated building) was always an important variety. During the last thirty years, the share of flue cured tobacco rose from 67% in 1970 to 77% in 1980 and 80% in 1988 (Goodman, 1993). An average of 5,5 kilograms of wood is used to flue cure one kilogram of green tobacco. However, some organizations state that tobacco growers have enough forest reserves on their own land (ITGA, 1997).

Government legislation and actions

After many accusations and pressure of NGO's and other groups a new Law on Agrochemicals was introduced in 1989 (Ley de Agrotóxicos, No. 7.802, 11/07/89). This law was very advanced with strict threshold limits and the prohibition of products with carcinogenic, mutagenic and teratogenic actions. Social or political pressure, however, did not continue, and this seems to have been accompanied by only a minimal compliance to the law (Hathaway, 1997). Furthermore, the responsible Ministries of Agriculture, Health and Environment enforced the following measures which reduced protection against toxic agrochemicals:
- previously rejected carcinogenic products (like amitraz) were registered for legal use;
- many dangerous pesticides from classes I and II were reclassified to less toxic classes III or IV;
- because of limited administrative capacity, checks on the use of pesticides, compliance to threshold limits and guidelines on residues were restricted to export products.

Production levels and the domestic use of agrochemicals increased, as did the number of deaths and intoxications. In 1994 Brazil, Argentina, Paraguay and Uruguay united in MERCOSUR[1] to promote economic integration and to coordinate legislation and

[1] The Common Market of the South (MERCOSUR) is an economic integration project in which Argentina, Brazil, Paraguay and Uruguay have been engaged, since 1991.
Its principal objectives are to improve the economies of their countries by making them more efficient and competitive and by enlarging their markets and accelerating their economic development by more efficient use of available resources; to preserve the environment; to improve communications; to coordinate macro-economic policies; and to coordinate the different sectors of the economies of the member countries.

other regulations. A subgroup on pesticide trade and registration was also formed. This group consists of representatives of the Ministries of Agriculture and Health. Non-governmental organizations or other direct representatives of agricultural field workers feel that they cannot participate in the negotiations, whereas the national pesticide industry can. The main decisions of MERCOSUR included the facilitation of the pesticide trade and the introduction of threshold limits for pesticide residues on food and in the environment.
Because of the new regulations, several highly toxic products are now commercially available, including metamidophos, monocrotophos and 2,4-D (Hathaway, 1997). It remains difficult for the government to regulate the threshold limits in practice, mainly due to the lack of interest on the part of responsible authorities, the absence of this topic on the political agenda, and the lack of repercussions. The state of Paraná, however, in comparison with other states, did conduct some forms of inspection, for instance on the aerial application of pesticides (Knight, 1997; Weid von der, 1997).

In areas where small farmers can organize themselves politically, farmers' unions work to defend their interests. For instance, in response to legal charges and as a result of meetings between union leaders and tobacco company representatives in 1995, tobacco companies in Sao Joao de Triunfo (a small region in southern Paraná) and the government adopted regulations regarding pesticides. Tobacco companies were required to provide appropriate clothing for those workers applying pesticides, to instruct farmers on how to dispose of empty pesticide containers properly, to collect empty pesticide cans and bottles from farms and to train farmers on the proper use of pesticides. The government committed itself to periodic blood tests to check contamination levels among farmers. Unfortunately, both the government and the tobacco industry only partially followed the agreements, and in 1998 the farmers' union once again went to court in an attempt to improve the situation (PANNA, 1998).

The future of tobacco

Farmers are beginning to question whether the large amounts of highly toxic pesticides are really necessary for the cultivation of tobacco (Cordeiro, 1998a). Positive results with organic food crop cultivation makes organic tobacco production more attractive. The Empresa Brasileña de Investigación Agropecuaria del Ministerio de Agricultura (EMBRAPA) introduced several products to biologically control plagues (such as the biological pesticide Bacillus thuringiensis) and introduced an official investigation on the large-scale use of alternative agricultural production methods. This investigation, however, is progressing very slowly, and results are not available yet (Weid von der, 1997). The Forum of Farmers' Organizations in the southern region of Paraná also has called for a sustainable agricultural system for tobacco.

Another option is the replacement of tobacco with cash crops. Most farmers, however, are skeptical about this, since farmers feel that the tobacco companies offer more security than they would receive from the government to grow food crops. The change to food crops requires credit, price guarantees and insurance for crop failures caused by the weather. Only with such governmental support can tobacco farmers change the situation. Until now, there have been no governmental regulations of this

kind (Cordeiro, 1998a).

The tobacco sector is permanently in search of new technological developments to improve productivity and quality (AFUBRA, 1997). Profigen, a Brazilian biotechnology company, is testing new technological developments and transgenic varieties of tobacco in Brazil. These new varieties, however, do not result in the use of fewer pesticides. Additionally, these new varieties form a threat to the wild relatives of the present tobacco varieties and are a source of genetic pollution with regard to the conserved native biodiversity (Cordeiro, 1998a).

The future of tobacco cultivation in Brazil is unclear. On a national level the tobacco sector plays an important role in the economic statistics on taxes, exports and employment (AFUBRA, 1997). Tobacco companies and powerful industries receive high profits from the sales of pesticides and chemical fertilizers. Local leaders believe that farmers' organizations still have a chance to change government policies. However, if one considers the situation at this moment, it seems unlikely that tobacco companies and other powerful industries and institutions will support any changes (Cordeiro, 1998a, Hickey, 1998).

Scientific research

In November 1999 a scientific study on the environmental and human health impacts of tobacco growing in Rio Grande do Sul will start, done by the National Cancer Institute (INCA) and the University of Santa Cruz do Sul (UNISC) in collaboration with the Canadian International Development Research Centre (IDRC). It will examine environmental and human health effects of both high and low levels of exposure to various agrochemicals and nicotine present on the tobacco leaves. The relationship between depression and the use of pesticides will be taken into account, and attention will also be given to social aspects. The research project will include toxicological analyses of blood and urine (on acetylcholinesterase levels, as explained in chapter 4), measurements of pesticide residues in water and food and neurological health examinations among tobacco workers. The final results can be expected August 2001.

Chapter 3 SUICIDE AND DEPRESSION

There are high suicide rates among farmers in many countries, for example Sri Lanka (Hoek van der, 1998), India (Verma, 1998), Egypt (PANNA, 1996), the USA (Stallones, 1990; Gunderson, 1993) and the United Kingdom (Dillner, 1994; Malmberg, 1997). This is considered to be a large-scale problem.
Some countries are known for high suicide rates in general. In Sri Lanka suicide rates reached 43 per 100,000 in 1992, one of the highest rates in the world (Hoek van der, 1998). The Scandinavian countries also have a long history of excessive suicide rates (Diekstra, 1993). Brazil, however, is not on this list. The general suicide rate in Brazil is approximately 3.20. Table 1 shows the mortality rates due to suicide (per 100,000 inhabitants) in 1989 for the 6 major states of Brazil. Both Rio Grande do Sul and Paraná are states with both important tobacco growing areas and other intensive agricultural areas. Both show elevated suicide rates. These figures have to be treated with care. Researchers point out that deaths are commonly noted as suicides, without due investigation into whether these are possibly unintentional suicides resulting from lethal accidental poisonings (Dinham, 1993). Information about the occurrence of depressive disorders in these states is not available.

Table 1. Suicide rates in the 6 major states of Brazil in 1989 *(Falk, 1996)*

State	Suicide rate
Brazil	3.20
Rio Grande do Sul	8.09
Paraná	5.25
Sao Paulo	3.99
Minas Gerais	2.95
Rio de Janeiro	2.06
Bahia	1.03

Risk factors for suicide

In general, more than half of the suicide attempts are due to depression, and although the depression may sometimes be endogenous, excessive suicide rates are often a result of reactive or neurotic behavior (Ed., 1992; Hoek van der, 1998; Isacsson, 1994; Parrón, 1996).
Many social and psychiatric factors can play a role in disposing people to commit suicide. Poverty, instability, constant stress and the absence of social controls can lead to suicide attempts (Berstein, 1991; Hoek van der, 1998; Verma, 1998). And also marital problems, psychiatric and physical illnesses, and alcohol and drug abuse dispose people to commit suicide (Hettiarachchi, 1989). There are clear correlations between religion, unemployment, divorce and crime rates (Diekstra, 1993). The easy availability of toxic substances and the publicity given to acts of suicide also play a role in high suicide rates (Hettiarachchi, 1989; Diekstra, 1993; Fernando, 1995).

Suicide and depression

Depression can range from occasional 'down' periods to episodes severe enough that hospitalization is needed. A person suffering from a *major depression* feels sad and hopeless for weeks or months, often losing interest in all activities and taking pleasure in nothing. Feelings of inadequacy, worthlessness or guilt are common. Changes in eating habits, lack of sleep, loss of concentration and clear thinking, and even delusions may occur as well.
In general, a more common pattern of depression is *dysthmia*, a milder form often lasting for a longer time, at least for a period of two years. A person is sad, lacks interest, and cannot enjoy life. Mental and behavioral disruption may be less severe. Both major depression and extremely intense dysthmia can lead to suicide attempts. Usually these people (95%) do not want to harm or kill themselves, but only want to communicate or express their feelings of despair, hopelessness, anger, frustration, self-hatred, or absence of long-term or meaningful life goals (Berstein, 1991; Diekstra, 1993).

Psychological theories of depression

There are several theories about the psychological causes of depression. Depressive disorders have been attributed to dependency needs, loss of significant sources of reward, and pessimistic patterns of thinking about oneself. Some of these problems may be inherited, though their occurence may be determined by a certain attributional style constituting the predisposition that makes a person vulnerable to depression. Additional features, such as a general tendency to draw negative conclusions about oneself, may also play an important role (Berstein, 1991).
In line with the objectives of this study, more attention will be paid to the physiological causes of depressive disorders.

Physiological theories of depression

Although the specific biochemical disturbances in mania and depression have not been definitely established, it is thought that multiple factors play a role (Janowsky, 1972). There is considerable evidence suggesting that monoamines, a group of neurotransmitters in the brain including norepinephrine (or noradrenaline), dopamine, and serotonin, are significant determinants of mood and behavior (Davis, 1970; Janowsky, 1974; Bernstein, 1991). Acetylcholine, a neurotransmitter in both the peripheral and central nervous system, has important functions in the affect (mood) area of the brain and areas involved in movement and memory.
Affective disorders (or mood disorders) are believed to be determined by a complex balance between adrenergic and cholinergic factors in those areas of the brain which regulate affect (Janowsky, 1972). This balance between cholinergic and adrenergic neurotransmitter activity also determines the direction and extent of body functions such as heart rate, gastric motility and tone and pupil size.
An excess of acetylcholine merely upsets the balance of transmitter systems playing a role in affective functions. Several studies indicate that depressed people have lower levels of norepinephrine or its chemical by-products then do other people (Crow, 1984).
Another mechanism is dopamine receptor hypersensitivity. In the *corpus striatum* in

the forebrain, a balance exists between dopamine as the inhibitory system and acetylcholine as the excitatory system. The dopaminergic system inhibits the cholinergic neurons and vice versa. Excessive acetylcholine suppresses dopaminergic activity, and hypersensitivity of post-synaptic dopaminergic neurons may result (Joubert, 1988). Direct or indirect dopamine receptor antagonists are found to decrease striatal acetylcholine levels (Consolo, 1975). According to this theory, depression develops from central cholinergic predominance in the affective system and mania is a disease of central adrenergic (or serotonergic) predominance in the affective system.

Chemicals causing depression

There is growing awareness that chemicals can have non-therapeutic effects on behavior, including depression. The behavioral effects of chemical agents are still being investigated. Because of many confounding factors, such as weak exposure data, differences in effect measurements, methodological errors and errors of analysis, they build up a base of inconsistent findings (Anger, 1998). Of the many chemicals studied in behavioral neurotoxicology, replicated findings have emerged only for carbon disulfide, styrene, trichloroethylene, organophosphate pesticides, lead manganese and mercury. The effects which have been tested most often are cognitive, motor and sensory function and affect/personality.
Chemicals that show positive findings in affect/personality tests in several scientific studies are:
- *carbon disulfide* (CS_2) (Hänninen, 1978; Tolonen, 1978),
- *organic solvent mixtures* (Cranmer, 1986; Escalona, 1995),
- *lead* (Baker 1984; Jeyaratnam, 1986; Maizlish, 1995),
- *mercury* (Istoc-Bobis, 1987; Forzi, 1976; Langworth, 1992),
- *organophosphate pesticides* (Stephens, 1995;Wesseling, 1997).

In the case of pesticide investigations and discussions are still in progress. There is more and more evidence that organophosphates poisoning can result in depression and other mood disorders because of toxicological changes in the central nervous system. This might play a significant role in the high suicide rates in intensive agricultural areas with elevated exposures to pesticides.

It is clear that suicide is a complex item and that it is often impossible to point to one specific cause. Moreover, research on the neurotoxicological origin of high suicide rates is complex and has to deal with many confounding factors. This is especially the case in this study. An attempt has been made to take into account as many factors as possible, but conclusions have to be drawn carefully and have to be placed in a broad perspective.

Chapter 4 TOXICOLOGICAL MECHANISMS

Two categories of pesticides are assumed to be capable of elevating cholinergic neurotransmitter levels in the central nervous system and thus disturbing the balance of neurotransmitters in the affective system. These pesticides are organophosphates and carbamates. Organochlorines are believed to have an effect on monoamine levels, another group of neurotransmitters in the brain.
In addition, there are several other groups of pesticides which to some extent have an effect on the central nervous system, including depression. Although these groups get less attention in epidemiological research on exposure to pesticides and depression, the toxicological mechanism of the most important groups will be discussed here: pyrethroid esters, ethylene dithiocarbamates, organomercurial fungicides, and fluoro-acetate and acetamide rodenticides. Almost all of these pesticides are used in tobacco cultivation worldwide.
Most pesticides affect both the peripheral and central nervous systems. One would suppose that when depression occurs, other neurorological effects would be noticeable. This, however, is not the case for any of the pesticides described.

Many other pesticides are not mentioned in this chapter. This does not mean exposure to these pesticides cannot result in depressive disorders. In most cases data simply are not available. For only of a small group of pesticides the toxic effects on humans are well known. For greater part, however, there is no clear picture of effects or threshold levels. Because there is no clear effect measure for depression in animal studies, basic toxicological research on depressive disorders in humans is even more difficult.

Organophosphates

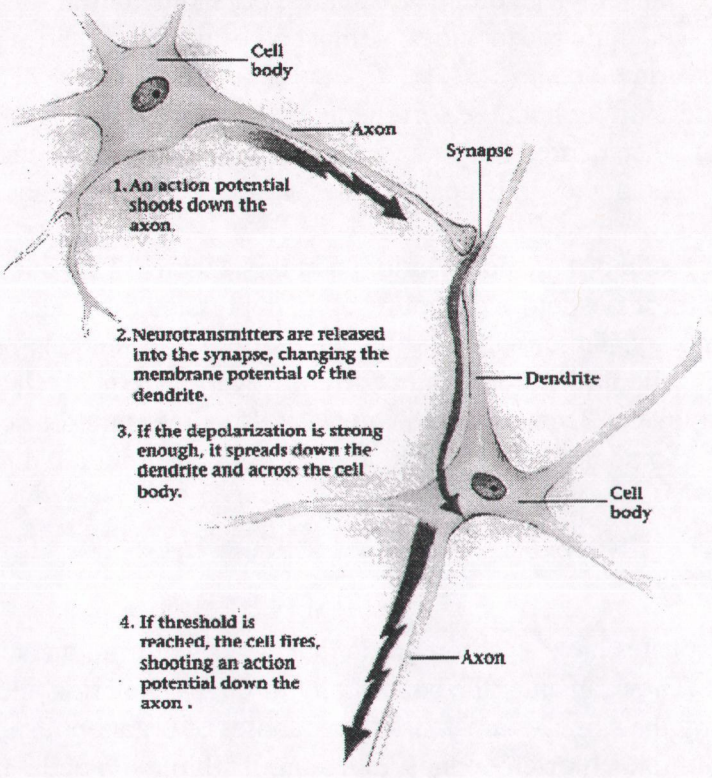
Organophosphates have a carbon group that is derived from an acid containing phosphorus. They can enter the body orally through inhalation and through absorption by the skin (Mearns, 1994). Examples of organophosphate insecticides include parathion, chlorfenvinphos, diazinon, fenthion, diamethoate, monocrotophos, and malathion.

Organophosphates (like carbamates) are cholinesterase-inhibiting pesticides and highly toxic for the nervous system.
Acetylcholine is a neurotransmitter transferring nerve impulses at cholinergic synapses throughout the nervous system. It is released at the presynaptic side and after binding to a receptor on the postsynaptic side it is broken down by the enzyme acetylcholinesterase. Acetylcholinesterase is always present in cholinergic synapses. Organophosphates have sites resembling acetylcholine and therefore can act as alternative substrates, binding irreversibly to the active side of the enzyme acetylcholinesterase. After the initial organophosphate acetylcholinesterase bonds are formed, a conformational change in the molecular structure of the organophosphate occurs. This strengthens the binding and makes the organophosphate acetylcholinesterase complex irreversible. This process is called 'aging' and occurs 12-36 hours after binding. The binding results in the disfunctioning of acetylcholinesterase and acetylcholine accumulates in the synapse. This buildup of acetylcholine results in overstimulation, which is followed by paralysis of synaptic

COMMUNICATION IN THE NERVOUS SYSTEM

The nervous system has three general functions: sensory, integrative, and motor. It can be divided into the *central nervous system* (the brain and the spinal cord) and the *peripheral nervous system* (the nerves that connect the central nervous system to other parts of the body). Its chief function is to carry messages within the brain or from one part of the body to another. The cells called *neurons* have a *cell body* and long fibers (*axons* and *dendrites*) and are specialized in communicating with one another (see figure 1).

Figure 1. Communication between neurons (*source: Bernstein, 1991*)

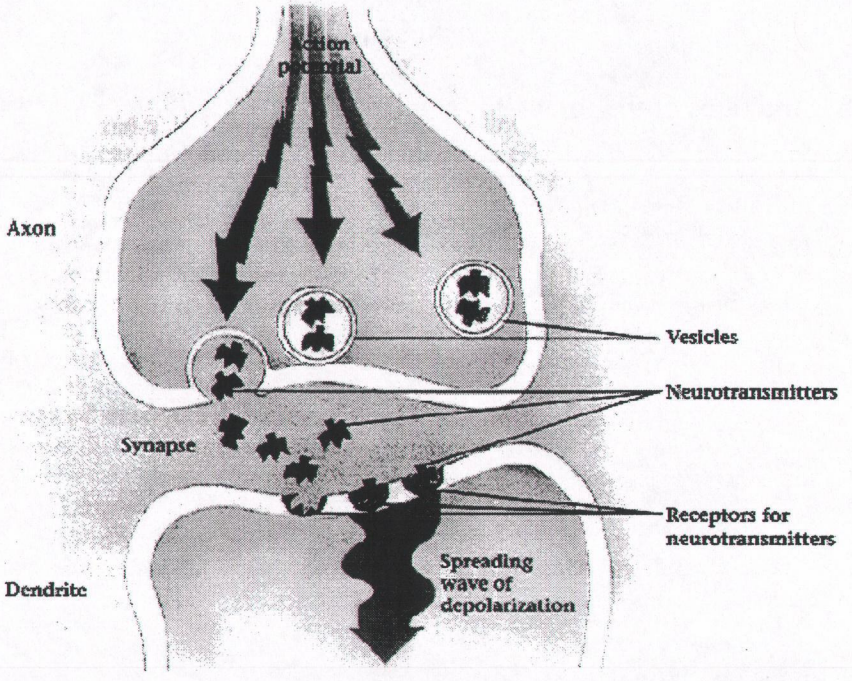


The transmission of a signal is based on an abrupt change in the electrical potential of the outer membrane of the cell. The inside of the cell is slightly negative compared with the outside, causing the outer membrane to be polarized. Positively charged sodium ions (Na^+) are highly concentrated on the outside of the cell. Much of the negative charge inside the axon is produced by negatively charged chloride (Cl^-), and a relatively small proportion of positively charged potassium ions (K^+). Sodium can pass the membrane by special channels which are normally closed. Stimulation of the cell causes *depolarization* near a particular sodium channel. When reaching a certain threshold the channel swings open, allowing positive sodium to rush into the axon. This stimulates the next gate to open, and so on down the axon. This is called the *action potential*. The cell is *repolarized* when the sodium channels are closed and gates are opened for potassium to flow out.

When the signal reaches the end of an axon the signal has to be transferred to another cell. The place of contact between two neurons is called a *synapse*. The transfer of information across a

synapse is accomplished by chemicals called *neurotransmitters*. They are stored in vesicles at the tips of axons. When an action potential reaches a synapse it modulates the enzyme responsible for the uptake and release of calcium across nerve membranes. *Calcium ions* (Ca^{2+}) flow into the end of the axon, and in response the *presynaptic neuron* releases a neurotransmitter. The neurotransmitter spreads across the synapse to reach the next *postsynaptic neuron*. There the neurotransmitter binds on a *receptor* and triggers a change in the membrane potential, thus creating an electric signal once again (see figure 2).

Figure 2. Neurotransmission in the synapse (*source: Bernstein, 1991*)



Normally a neurotransmitter stays at the receptor site only briefly before it is removed. An enzyme may brake down the neurotransmitter, but more commonly the neurotransmitter is transported back into the presynaptic cell by a process called reuptake. When the neurotransmitter is not removed the binding at receptor sites continues and hyperstimulation of the postsynaptic neuron occurs.

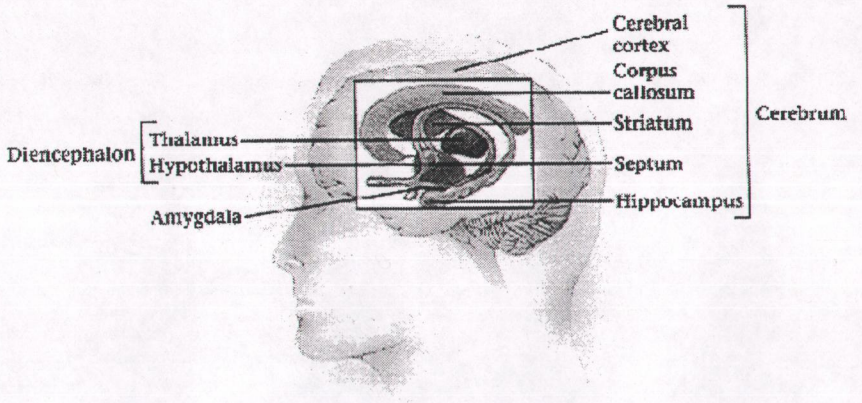
The brain is the largest and most complex part of the nervous system. It is composed of about one hundred billion neurons and innumerable nerve fibers which communicate with one another and with neurons in other parts of the system.
The brain contains nerve centers associated with sensory functions and is responsible for sensations and perceptions. It issues motor commands to skeletal muscles and carries on higher mental functions, such as memory and reasoning. It also contains centers that coordinate muscular movements and regulate visceral activities. In addition, the brain also provides information which determines personality.
The *limbic system* is located in the forebrain and plays an important role in the regulation of emotion and memory. The system includes the hypothalamus, the hippocampus, the septum and the amygdala (see figure 3).
At least fifty chemicals occur naturally in the brain, acting as neurotransmitters. Different sets

of neurons use different neurotransmitters, and different neurotransmitters occur in different pathways and structures.

The most important neurotransmitters and their normal function are:

acetylcholine	*movement, memory*
norepinephrine	*sleep, learning, mood*
serotonin	*mood, appetite*
dopamine	*movement, reward*
GABA (gamma-amino butyric acid)	*movement*
glutamate	*memory*
endorphins	*modulation of pain*

Figure 3. Structures of the forebrain (*source: Bernstein, 1991*)



sources: Bernstein, 1991; Shier, 1996

transmission (Hayes, 1991). In the cortical parts of the brain this results both in a disturbance of the balance of transmitter systems and in a hypersensitivity of dopamine receptors, as described in chapter 3.

Nerve impulses may be blockaded in the central nervous system, at the autonomic ganglia, and at the skeletal muscle-nerve junctions. The acute effects (after 4 to 12 hours after exposure) are well-known and include muscle fasciculations, cramps, generalized muscle weakness, depression of respiratory drive, delirium, loss of consciousness and seizures. Hyperstimulation of the parasympathetic system results in diarrhea, urination, miosis, bronchospasm, emesis, lacrimation and salivation. Recent data have also suggested visual changes, pancreatitis, neurobehavioral changes, hypertonicity, anxiety, irritability, loss of memory and acute psychosis. Relevant for this research is that high levels of acetylcholine are believed to induce two forms of psychiatric illness in the longer term: depression and schizophrenia (Gerhson, 1961; Hayes, 1991).

Maximum cholinesterase depression occurs from 8 to 24 hours after exposure, and it may take up to three months for cholinesterase levels to stabilize (Mearns, 1994). Blood plasma cholinesterase and red blood cell (RBC) cholinesterase levels provide a

measure of inhibition. Plasma cholinesterase levels decline and return to normal faster than RBC levels. This plasma enzyme is produced by the liver and has base-line fluctuations which are due to many variables. It can take 7 to 60 days to return to levels found prior to organophosphate insecticide exposure. RBC cholinesterase activity regenerates more slowly because new RBC's must be released from the bone marrow, and renewal can take up to 60 to 90 days. The less fluctuating RBC cholinesterase is the preferred measurement for documenting and monitoring exposure (Schenker, 1998).
Symptoms of organophosphate insecticide toxicity are usually not seen until 50% of baseline cholinesterase activity is inhibited. But this is not a reliable threshold. In addition, the large variability in normal cholinesterase levels makes the interpretation difficult. No clearly reliable association has been established between the magnitude of serum cholinesterase decrease and the severity of poisoning (Schenker, 1998). Nor can a threshold be given for the occurrence of depression. Cases of depression due to exposure to pesticides are most often reported after organophosphate pesticide poisonings (Gershon, 1961; Joubert, 1988). Poisoning means damage or disturbance caused by poison and includes intoxication. Cases of depression due to exposure to pesticides without symptoms of poisoning are reported less frequently.

In addition to inactivating the acetylcholinesterase enzyme, organophosphates can also inhibit the neuropathy target esterase enzyme (NTE), causing distal sensory-motor axonopathy (organophosphate induced delayed polyneuropathy). Characteristic manifestations include weakness, paralysis, and paresthesia in the distal lower extremities. An intermediate syndrome includes weakness of proximal limb muscles and respiratory muscles and cranial nerve paralysis. These findings, however, do not relate to depression.

Carbamates

Carbamates are another group of cholinesterase inhibitors. The carbamate insecticides are readily absorbed by inhalation, ingestion or through the skin and are often used in combination with an organophosphate or pyrethroid insecticide. Aldicarb, oxamyl, and methamyl are highly toxic carbamate insecticides. Other carbamates such as dioxacarb and carbaryl are less toxic.

Unlike the organophosphates, N-methyl carbamate esters bind reversibly to the binding sites of the enzymes acetylcholinesterase and neuropathy target esterase and do not produce aging reactions. The carbamylated acetylcholinesterase enzyme can undergo spontaneous hydrolysis, which reactivates the enzyme (Schenker, 1998). Therefore, carbamate poisonings are usually shorter in duration and less severe than organophosphate poisonings. Central nervous system toxicity is less predominant because the N-methyl carbamates do not fully penetrate the blood-brain barrier. It is assumed that they are unlikely to cause persistent effects on the central nervous system or delayed peripheral neurotoxicity (Hayes, 1991). However, only very few carbamates have been submitted to extensive neurotoxicity testing (Ecobichon, 1994).
There are several case reports on chronic neurotoxic effects from carbamate poisoning (Branch, 1985; McConnel, 1994), but only one study showed epidemiological evidence for persistent neurological effects from carbamate

poisonings (Wesseling, 1997). Stress might be a factor in enhancing any neurotoxic effect. It has been observed in rats that stress increases the permeability of the blood-brain barrier with regard to the carbamate compound pyridostigmine by a factor of 100 (Friedman, 1996).

Organochlorines

Organochlorines can be classified in several groups of chemical structures. They all are very persistent, are easily absorbed through the lungs, the gastrointestinal tract and the skin and, they accumulate in organs, including fat and tissue. Examples are DDT, lindane, benzene hexochloride, aldrin, endosulfan, heptachlor, dieldrin and mirex.

The mechanism of toxicity is related to the ability of the organochlorines to alter ion fluxes, principally in nerve tissue. One of the alterations caused by DDT-like agents (the dichlorodiphenylethanes) is a delay in sodium channel inactivation. This results in a prolongation of the falling phase of the reaction potential. Because of these negative afterpotentials, the nerve becomes extremely sensitive to small stimuli. Signs of poisoning include disturbances of sensation and coordination. Other symptoms are anorexia, headaches, tremors, motor hyperexcitability, anxiety, muscular weakness and fatigue (Ecobichon, 1995).

The other organochlorine insecticides (cyclodienes, chlorinated benzenes and cyclohexanes) have different mechanisms of action which appear to be localized in the central nervous system. These agents mimic the action of picrotoxin, a nerve excitant and also an antagonist of the neurotransmitter δ-aminobutyric acid (GABA). GABA induces the uptake of chloride ions by neurons. When picrotoxin or a cyclodiene insecticide interact with the GABA receptor, the chloride uptake is blocked and the partially repolarized nerve is left in a state of uncontrolled excitation. In addition to this, cyclodiene insecticides inhibit Na^+/K^+ ATPase and Ca^{2+}/Mg^{2+} ATPase, this last enzyme being important for the uptake and release of calcium across nerve membranes. This enzyme is located in synaptic membranes, and inhibition results in the accumulation of free calcium in the presynaptic regions of the neurons and the promotion of the calcium-induced release of acetylcholine from storage vesicles. In addition to enhancing neuronal activity, this can also result in a disturbance of neurotransmitter balances in the brain, as discussed in chapter 3, resulting in changes in affect.
The toxidrome includes disturbances of sensation, coordination, and mental status such as confusion, insomnia, anxiety and irritability. Other symptoms are anorexia, malaise, headaches, tremor, hyperreflexia, motor hyperexcitability, and muscle weakness.
Only mirex, a chlordecone, is thought to induce depression after chronic toxicity (Ecobichon, 1995; Schenker, 1998).

Pyrethroid esters

Pyrethrum is one of the older natural insecticides still in use. It is an extract made from flowers of the chrysanthemum and containing a mixture of six different esters of chrysanthemic of pyrethric acids. Synthetic pyrethroid derivatives are cheaper, less

biodegradable, have a rapid biotransformation in mammals, and allow a broad use of this type of insecticides. Commercial pyrethroid products often contain organophosphate or carbamate compounds and compounds that protect against degradation. They have a low mammalian toxicity. The major route of exposure is dermal. There has been no indication that either acute or chronic exposure to the natural products is likely to produce significant neurologic changes in humans (Ecobichon, 1995).

Synthetic pyrethroids are divided into two classes, based on either function or clinical effects. Pyrethroid type I includes allethrin, permethrin and cismethrin; pyrethroid type II includes fenvalerate, deltramethrin and cypermethrin. The synthetic esters increase peripheral nerve excitability in the same way as does the organochlorine compound DDT. All esters increase nerve excitability by delaying sodium channel inactivation. Type II pyrethroid has the strongest effect and also binds and blocks the GABA receptor and inhibit Ca^{2+}/Mg^{2+} ATPase. Like clorodiene compounds this leads to elevated levels of acetylcholine in the synapse (Schenker, 1998). Theoretically, this could lead to depressive disorders. Literature on pyrethroid-induced depression in humans, however, is not available. The reported effects from large absorbed doses are loss of coordination, tremor, salivation, vomiting, diarrhea, and contact dermatitis (Hayes, 1991).

Ethylene dithiocarbamates

Ethylene bisdithiocarbamates are a class of fungicides which includes maneb, mancozeb and zineb. They have a metal compound, usually manganese or zinc. The ethylene bisdithiocarbamate pesticides degrade into ethylene thiourea (ETU). This compound is mutagenic, carcinogenic and teratogenic. It also has antithyroid activity. There is a potential interaction with alcohol resulting in toxic metabolites and an intolerance to alcohol (Hayes, 1991). The combination with alcohol creates the most dangerous situations.

Dithiocarbamatic acid degrades into carbon disulfide, and this compound is believed to cause a toxic effect in human. The main effects are the reduced uptake of iodine, thyroid disfunctioning, and hepatic damage. Skin exposure can result in allergic dermatitis. Acute and chronic poisonings from dithiocarbamate fungicides result in obvious, immediate and persistent neurologic signs and symptoms, involving both the peripheral and the central nervous systems (Ecobichon, 1995, Hayes, 1991). These effects, however were reversible and of short duration (Hayes, 1991). Neurologic effects in the central nervous system might be caused by an increase of dopamine (Ferraz, 1988).

Methyl bromide

Methyl bromide is a widely-used bromomethane fumigant, used, for example, with dry foodstuffs, in wood conservation and as a soil fumigant against nematodes, fungi and weeds. The toxicity of methyl bromide can be caused by the compound itself or by its hydrolysis products bromine and methanol. Target organs are fat tissue, lung, liver, adrenals, kidney and brain. Neurotoxic effects are caused by the methyl bromide compound itself, and include a decrease in the levels of norepinephrine.

The mechanism of the *in vitro* action of methyl bromide is a chemical reaction which irreversibly inhibits a number of SH-enzymes. Initial immobilization can be caused by the reversible breakdown of ATP.
High concentrations of methyl bromide can produce rapid unconsciousness during exposure, leading to a sudden 'anesthetic' death. Most cases, however, are characterized by delayed onset, a great variety of symptoms, and delayed recovery, if death by circulatory failure does not occur. Central nervous system manifestations appear after common initial symptoms and include numbness, tremor, great agitation, change of personality, coma and convulsions.
The most important route of exposure is respiratory, but dermal exposure can also produce systemic and severe illness (Hayes, 1991).

Organomercurial compounds

The organomercurial alkyl and aryl derivatives are used as fungicides to prevent seed-borne diseases of various crops such as grains, vegetables, cotton, soybeans and fruits. Compounds of each group of organomercury fungicides involve a wide range of inorganic or organic anions. The availability of organic mercury compounds for absorption is largely determined by vapor pressure. Consumption of contaminated fish is an important factor in nonoccupational exposure (Hayes, 1991).

Alkyl and aryl mercury compounds are mainly transported by the erythrocytes in the blood. Effects arise essentially from the mercuric cation. Inhibition of protein synthesis is one of the earliest biochemical effects (Hayes, 1991). Chronic poisoning eventually involves most of the organs to some extent. However, the major effects of ethyl mercury are associated with the peripheral sensory and motor nerves and the central nervous system, including emotional instability. These include irritability, fits of anger and agitation. There is strong evidence for a causal relationship between blood mercury levels and depression (Hayes, 1991; Ecobichon, 1995). Even in mild poisonings symptoms often persist for years. The effects of adult exposure versus prenatal exposure differ markedly. In the developing nervous system, cell division is disturbed and brain abnormalities and mental retardation often occur (Hayes, 1991).

Fluoro-acetate and acetamide

Fluoro-acetate and acetamide are extremely toxic rodenticides. Fluoro-acetate pesticides are absorbed by the gastrointestinal tract, and fluoro-acetamide is usually absorbed by the skin. Both are intensely poisonous for mammals, but investigators agree that fluoro-acetamide is less toxic than is fluoro-acetate.

The mechanism of action for both pesticides is the same and involves incorporating fluoroacetate into fluoroacetyl-coenzyme A, which then condenses with oxalacetic acid to form fluorocitrate. This product inhibits the enzyme aconitase, which is responsible for the conversion of citrate to isocitrate. The build-up of fluorocitrate blocks the tricarboxylic acid (Krebs) cycle, resulting in lowered energy production, reduced oxygen consumption, reduced glucose metabolism, reduced cellular concentrations of ATP, and an accumulation of citrate in the tissues. The blockage of energy metabolism has many toxic effects. One of them is the increased tissue and

plasma concentration of citrate. These concentrations are responsible for a decrease in ionized calcium levels in the blood, which play a role in the depolarization of neuromembranes (Hayes, 1991). The main toxic effect is on the central nervous system and the heart, but several other effects can also occur. Ingestion leads to nausea, vomiting and abdomal pain, replaced by hypotension, sinus and ventricular tachycardia, renal failure, and muscle spasms. Effects on the central nervous system include anxiety, agitation, stupor, seizures and coma. There are signs of cerebellar degeneration and atrophy (Ecobichon, 1995).

Mixtures

Simultaneous exposures to two or more active ingredients occur frequently among agricultural workers. This exposure to mixtures might influence the toxicity of individual chemicals and can create an synergistic (additional or superadditional) or an antagonistic effect. Concomitant exposure to two or more anticholinesterase agents usually produces an additive effect, but potentiation may ensue (Stacey, 1993). Potentiation might be due to the inhibition of carboxylesterase which prevents the inactivation of organophosphorous compounds containing a carboxylester function.
Pyrethroids are probably metabolized by the same carboxylesterases, and potentiation of their toxicity might occur with combined exposure to certain organophosphates as well.
Impurities in pesticide formulations can have the same potentiating effect or induce a different kind of toxicity.
Much is still unknown about many of the interaction mechanisms and their outcomes. Furthermore, a multiple exposure to several other chemical or physical agents (occupational or non-occupational) can also increase the complexity of risk assessment (Henderson, 1995).

Toxicant-induced loss of tolerance

Another biological mechanism is discussed in a number of works of neurotoxicology, occupational medicine and biological psychiatry. Some researchers have developed a model for Multiple Chemical Sensitivity based on olfactory-limbic dysfunction and overlapping in part with Post's kindling model for affective disorders. According to this theory, a two-step process occurs. First, an initial salient exposure event(s) interacts with a susceptible individual, causing loss of tolerance. This can be a one-time, intermittent or continuous exposure to pesticides, solvents, or air contaminants. Second, formerly well-tolerated substances, such as low-level chemical inhalants (for instance, car exhaust or cleaning agents) as well as food, drugs, alcohol and caffeine trigger symptoms which can lead to a broad spectrum of chronic illnesses. These illnesses are, for instance, depression, asthma, migraine and chronic fatigue (Davidoff, 1996; Miller, 1996; Miller, 1997; Davidoff, 1998). An explanation may be found in an increase in the number of cholinergic receptors, making an individual more sensitive to nicotine and muscarinic agonists. It is assumed that cholinergic super sensitivity is a state predisposing individuals to depressive disorders (Overstreet, 1996). However, this mechanism is yet to be proven. Nonetheless, it is clear that much still needs to be known about the various possible ways of action and many questions have to be answered.

Chapter 5 EPIDEMIOLOGICAL STUDIES

Approximately fifteen years after the introduction of organophosphate pesticides, the first case reports of pesticide-induced depression were reported by Gershon and Shaw (1961). Since then several other cases have been reported (Dille, 1964; Branch, 1986; Joubert, 1988). Only since the Eighties have epidemiological studies been performed which include the relationship between exposure to pesticides and depression or suicide.
These epidemiological studies can be divided into three categories: 1) studies on chronic exposure to pesticides and suicide; 2) studies on chronic exposure to pesticides and depression; and 3) studies on acute exposure to pesticides and depression.

Suicide due to exposure to pesticides is assumed to be the result of a state of depression. Because depression occurs first, studies measuring depression instead of suicide could give a better indication of the relationship.
Biomonitoring would be an even better measure. Psychophysiological effects, such as electrophysiological and endocrinological changes, reflect the underlying biochemical processes on which behavior depends. However, when using psychophysiological indicators for effect measurements, one needs accurate knowledge about causal psycho-biological relationships. Until now information has been lacking. Organophosphates are well known as cholinesterase inhibitors, and the effect of the accumulation of acetylcholine is well-established. However, the causal relationship between depression and organophosphates remains unclear.
Nevertheless, elevated blood levels of acetylcholine are used both as an indicator for exposure and as an effect measure.

Epidemiological studies on pesticide use and suicide

Few epidemiological studies have directly investigated the causal relation between the use of organophosphates and the occurrence of suicides (Table 2). A cohort study done by Green (1987) on suicide among male forestry workers applying phenoxy acid herbicides in Canada revealed a significantly elevated Standardized Mortality Ratio[2] (SMR) of 212. A time-trend study done by Falk (1996) revealed suicide trends which coincided with spraying seasons in tobacco communities in Brazil. Parrón (1996) executed a regional comparison in Spain and found a significant odds ratio[3] (OR) of 3 for the area with an intensive use of organophosphates. In a case-control study done in Canada, Pickett found no strong support for the link between pesticide use and suicides (1998). Only the comparison between two subgroups 1-14 acres versus 0 acres sprayed with insecticides showed a significant OR of 1.71.

The main problem in these studies is the difficulty of excluding confounding factors. Because suicide is such a complicated cause of death which can be influenced by so

[2] The Standardized Mortality Ratio is a measure for mortality in the study population standardized for age distribution in the standard population. A SMR of 100 means no difference in mortality among study population and standard population.

[3] The odds ratio is an indicator used to compare the prevalence of exposure among cases and controls. An odds ratio of 1 means that there is no difference in exposure among the different groups.

many factors, it is very difficult to draw definite conclusions. Moreover, suicide is often underreported (Monk, 1987; Hettiarachchi, 1989; Wesseling, 1993; Keifer, 1996; RAP-AL, 1998).
Because the number of studies is too small and the confounding factors are too numerous, definite conclusions cannot be drawn. But these studies strengthen the hypothesis that exposure to pesticides is a risk factor for suicide.

Epidemiological studies on pesticide use and depression

Relatively few epidemiological studies are available in literature dealing with behavioral changes such as chronic neurologic sequelae due to exposure to organophosphate pesticides. These sequelae includes three functional systems of neurobehavior: 1) the capacity of the nervous system to deal with information; 2) feelings, emotions, and motivation; and 3) a control function which determines how behavior will be expressed.
In most investigations much attention has been paid to cognitive and performance effects, such as memory, reaction time, and attention. When depression was measured it was usually part of tests for mood disorder. An overview of epidemiological studies on long-term sequelae of exposure to pesticides which took 'depression' into account is given in tables 3 and 4.

Exposure data

Assessing exposure is not only a very important part of an epidemiological study but also the most difficult part. To evaluate the quality of the studies available and the methods for exposure assessment, a brief summary is given.

In studies of acute pesticide poisoning, cases were selected from official registers. For most of these cases information was available on the kind of pesticide; only organophosphorous poisonings were taken into consideration. Melius (1981) studied a group of firemen who had several negative health effects after a fire in a pesticide warehouse. Savage (1988) and Steenland (1994) took occupational and non-occupational registered poisonings; Rosenstock (1991) and Reidy (1992) used only hospitalized occupational poisonings; and Wesseling (1997) reported on intoxicated banana workers. In the case of occupational poisonings, it is very likely that these individuals also had a chronic low level of exposure to pesticides at work. This combination of exposures should be taken into account when drawing conclusions.
In all studies controls were defined differently as well. Wesseling (1997) and Melius (1981) used a pesticide-exposed group from the same work area, but without poisonings. Rosenstock (1991) used male friends or siblings who were never poisoned. Savage (1988) and Steenland (1994) used subjects who never worked with pesticides. The background of Reidy's (1992) controls is unclear.

Long-term exposure studies were performed among agricultural workers who applied pesticides (organophosphates, carbamates, among others), malaria control sprayers (DDT) or sheep dip farmers (organophosphates and pyrethroids), mostly in western countries (Ames, 1995; Stephens, 1995; Stokes, 1995; Fiedler, 1997; van Wendel de Joode, 1999; Pilkington, 1999). In most of these studies exposure was estimated on the basis of years of employment and/or job history. More reliable group or

individual exposure levels were not available for these studies. There is often no difference in these studies between kinds of pesticides and the influence of other exposure-related variables such as the use of protective clothing and other work practices, the use of other chemicals and other exposure routes, none of which can be assessed in detail. Only Pilkington's study (1999) included an exposure assessment based on a neuropathy questionnaire and a sensory test. This method also generated the control group. In all other long-term exposure studies, controls were found among subjects working in other occupations, if possible in the same area. Questionnaires were used to compare groups on confounding variables and to reveal exposure to pesticides among control-groups. Only Stokes (1995) matched individually.

Measuring depression

There are many questionnaires for medical purposes which focus on the individual and his or her functional and emotional capacity (Gamberale et al, 1990). For occupational health purposes, however, the only interest is a statistical probability of a change in a depressed mood. Depression usually is embedded in a larger range of mood disorders. Tests used in the relevant epidemiological studies were Minnesota Multiphasec Personality Inventory-1 and -2 (MMPI-1 and MMPI-2), Questionnaire-16 or Scandinavian Questionnaire (Q-16), Brief Symptom Inventory (BSI), the Profile of Mood States (POMS), and the Hospital Anxiety and Depression Scales (HAD). Stephens et al (1995) used the General Health Questionnaire.

The MMPI-1 and MMPI-2 include hypochondriasis, depression, hysteria, psychopathic deviate, masculinity-femininity, paranoia, schizophrenia, hypomania and social introversion measured on a clinical scale (Hathaway and McKinley, 1989).
The Questionnaire-16 or Scandinavian Questionnaire includes self-reporting of difficulties in memory and concentration, and symptoms of headache, fatigue, depression and irritability. Answers are 'yes' or 'no' and, evaluation is done by the number of positive answers (Hogstedt et al, 1984).
The Brief Symptom Inventory contains nine psychopathological dimensions: somatic symptoms, obsessive-compulsiveness, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation and psychoticism (Derogatis and Spencer, 1982). It uses a five point scale ranging from 'not-at-all' to 'extremely'.
The Profile of Mood States is part of the computerized Neurobehavioral Evaluation System-2. It contains 65 adjectives that describe five different moods: tension, depression, anger, fatigue and confusion (Letz, 1988). Subjects are asked to indicate their moods for one week on a five-point scale ranging from 'not-at-all' to 'extremely'.
The Hospital Anxiety and Depression Scale assesses the frequency of symptoms to both anxiety and depression (Snaith, 1983). The maximum score attainable for both anxiety and depression is 18.
The General Health Questionnaire is a different kind of test. It assesses the individual's vulnerability to psychiatric disorder. The version with thirty questions regards reporting at least five symptoms as an indicator of depression (Goldberg, 1985).

Translations of mood tests must be done carefully and should take into consideration the subtle nuances in adjectives used to describe moods. Since every language uses

its own words to describe a mood, culture and language have to be taken into account. For instance, there are fewer Finnish adjectives for depression, so the Finnish version of POMS has a shorter Depression Scale than the original English version (Johnson, 1987).
Dichotomous outcome variables simplify test methods, but presumably result in less (non-differential) misclassification and therefore produce stronger associations (Wesseling, 1999).
In the investigations mentioned above many different tests were used. All tests are well-established and used extensively in in-depth neuropsychological assessments. There are, however, differences in cut-off points, sensibility and validity.

Conclusions of epidemiological studies

Epidemiological studies on suicide and exposure to pesticides tend to reveal a positive association. There are many differences in methodologies and sample sizes, and there are many possibilities for bias. Therefore, conclusions on causal relationships are hard to make.

Most evidence was found for depression resulting from acute high level of exposure to pesticides, mainly organophosphates. Although studies found in literature all had different methodologies and although they all showed positive results for neurotoxicity, conclusions related to depression were less consistent. However, five of the six studies analyzed show positive associations. Within studies contradictions could be found. Cases in Rosenstock's study (1991) had significant differences in BSI compared to controls. Within the same cohort, the Questionnaire-16 gave no significant results. This can be explained by the nature of the tests. Results from van Wendel de Joode (1999) revealed just the reverse. This strengthens the point that more research about test validity and sensibility is desirable.

Among the long-term exposure studies, Stephens (1995), van Wendel de Joode (1999) and Pilkington (1999) found positive relations between pesticides and depressed mood.
Stephens (1995) looked at long-term exposure to the group of organophosphates and used the General Health Questionnaire as an indicator of depression. It can be assumed that, with the General Health Questionnaire, positive relations can be found in an early stage. Reasonable sample size could also have had a positive influence on revealing the effect.
Van Wendel de Joode (1999) worked with sprayers in Costa Rican malaria control programs. Inside application of large amounts of mainly DDT (an organochloride), no use of personal protective equipment, and other dangerous practices suggest a relatively high exposure. Both the occurrence of depression and the total score were found to be significantly elevated by the Brief Symptom Inventory. The total score of the Questionnaire 16, however, was not significant.
Pilkington (1999) performed a detailed study among sheep dip farmers. Subjects were categorized in 'none', 'possible' and 'probable/definite' for the likelihood of neuropathy, and depression was measured by the Hospital Anxiety and Depression Scale. The categorization by other pesticide related effects was taken as a measure for exposure. This elucidates individual differences in susceptibility. Actually, the correlation between neuropathy and depression is measured. This might explain the

strong outcome of the study.
Other long-term exposure studies showed no relation between exposure to pesticides and depression. These studies were executed in the United States of America. It can be assumed that other kinds of pesticides are used there and that, due to other techniques, exposure is relatively low. However, personal protection was not always used and it is hard to assess the real influence of the type of country in which the studies were executed.

In summary, there is substantial epidemiological evidence for a causal relationship between depression and acute pesticide poisonings. This is especially the case for organophosphates, and probably for organochlorates and carbamates. A causal relationship between depression and chronic low levels of exposure to pesticides was less demonstrable. There are contradictions between studies, and no hard evidence for either affirmation or negation can be found. This stresses the need for further epidemiological research with more precise exposure data and better methods for measuring depression

Table 2. Overview of epidemiological studies on suicide and exposure to pesticides

Study	type of study	Exposure	Cases	n cases	Results	remarks
Green 1987 Canada	Cohort	Phenoxy acid herbicide application	multiple testing for cause of death	1.222 male forestry workers	SMR 212 (95% CI 126-298)	suicide risk decreases with years in forestry
Falk 1996 Brazil	time-trend	Organophosphate spraying season over 17 years	suicides registered by the Núcleo de Infromações em Saúde	196 cases in 1 state	suicide rate follow coincide with spraying seasons	could not exclude many confounding factors
Parrón 1996 Spain	Region comparison	Intensive agricultural area with high OP use compared to extensive open air agricultural area and industrial area	suicide cases from National Institute of Statistics over 12 years, incidence of mood disorders from Mental Health district data	3 areas	suicide: OR=3 (95% CI 1.17-8.73) mood disorder: OR=1.88 (95% CI 1.42-2.49)	strong association between suicide and exposure to pesticides is possible
Pickett 1998 Canada	case-control	From Canadian Census of Agriculture database: acres sprayed with herbicides; acres sprayed with insecticides; Cost of agro chemicals purchased	suicide between 1971-1987 from Canadian Mortality Database	1.457 farmers	OR=1.71 (95% CI 1.15-2.46) for subgroup: 1-48 vs. 0 ac. sprayed with insecticides	no strong support for biologically plausible link; other risk factors such as seasonal work and loneliness

BSI Brief Symptom Inventory
CI Confidence Interval
MMPI Minnesota Multiphasic Personality Inventory
NES Neurobehavioral Evaluation System
OP Organophosphate
OR Odds Ratio
POMS Profile of Mood States
Q-16 Questionnaire 16 (including depression)
RBC Red Blood Cell

Table 3. Overview of epidemiological studies which took into account the relationship between depression and acute pesticide poisoning

Study	type of study	Exposition	effect related to depression	n cases	Results	remarks
Melius 1981 USA	case-control	health effects at a fire at a pesticide warehouse	POMS: tension, depression, anger, vigor, fatigue and confusion	13 firemen	all significant except anger; Depression ($p<0.05$)	mixture of pesticides during long and smoky fire
Reidy 1992 California	Retrospective	documented clinical acute poisonings from phosdrin, lannate and maneb	Neurotoxic Anxiety and Depression Scale constructed from MMPI	21 farm workers	cases report more depression than do controls (66.7 vs 0%)	cumulative exposure from both acute and continuous low level exposure during field work
Rosenstock 1991 Nicaragua	retrospective	hospitalized occupational poisonings by OP's	Q-16 (including depression) and BSI for POMS	38 males	BSI not significant; Q-16 total was OR=2.5 (95% CI 1.0-4.1)	role of depression in 16 symptoms unclear
Savage 1988 Texas and Colorado	case-control	previously experienced acute OP poisoning	MMPI by cases and relatives' assessment	100 persons	cases: depression not significant, but validity, defensiveness, paranoia and social introversion were. relatives' assessment: depression was significant	mild neuropsychological deficits apparent in poisoned subjects' everyday functioning
Steenland 1994 California	case-control	from register: acute poisoning from OP's between 1982-1990	POMS: tension, depression, anger, fatigue and confusion	128 males	depression not significant; significant were tension (p .02) and confusion (p. 01)	also significant effect in tests on peripheral nerve function
Wesseling 1997 Costa Rica	case-control	banana workers with previous occupational OP or carbamate poisoning	Q-16 (incl. depression) and BSI for POMS	81 banana workers	BSI-total significant R^2 =22.4 (95% CI 10.4-34.4), in subset OP exposed: depression OR=2.9 (95% CI 1.3-6.6); Q-16 significant R^2=2.5 (95% CI 1.1-4.0)	also studied recent cholinesterase inhibition

Table 4. Overview of epidemiological studies which took into account the relationship between depression and long-term exposure to pesticides

Study	type of study	exposition	effect related to depression	n cases	Results	remarks
Ames 1995 California	case-control	prior history of documented RBC or plasma cholinsterase inhibition among workers applying pesticides without poisoning	POMS, part of NES2: tension, depression, anger, fatigue and confusion	45 workers appl. pesti-cides	no significant changes in the mood scales	no evidence for relation between moderate OP and carbamate exposure and chronic or long term neurologic sequelae
Fiedler 1997 New Jersey	retrospective cohort	exposure metric based on interviews and questionnaire on long-term use of OP's, activities and protective equipment - no history of acute poisoning	MMPI-2 test, including depression	57 tree fruit farmers	depression not significant	supports the idea that a poisoning or high dose exposure may be more deleterious to neurological function than chronic subacute exposure
Pilkington 1999 UK	case-control	based on neuropathological tests; 3 groups: none, possible, and probably/definite for the likelihood of neuropathy among sheep farmers using OP	Hospital Anxiety and Depression Scale	59 farmers in sheep dip area	depression was significant (p=0.000)	exposure categorization based on neuropathological effects
Stephens 1995 UK	retrospective cohort	retrospective exposure questionnaire on long-term exposure to OP's	vulnerability to psychiatric disorder by General Health Questionnaire	146 sheep farmers	significant OR=1.5 (95% CI 1.31-1.69)	not dose related; role of other social and economic factors unclear; no differences in cognitive tests
Stokes 1995 New York State	retrospective cohort	off/on season licensed workers applying pesticides	self reported depression, off and on season	81 workers appl. pest.	not significant	likely to have low exposure, no poisonings reported
van Wendel de Joode 1999 Costa Rica	retrospective cohort	previous occupation as DDT sprayer for malaria control	BSI and Q-16	29 malaria control sprayers	BSI depression significant OR= 0.5 (95% CI 0.2-0.8); Q-16 total not significant	also significant effect in tests for peripheral nerve function

Chapter 6 PESTICIDE POISONINGS

Because of the suspected relationship between organophosphate pesticide poisonings and mental problems such as depression, an evaluation of the occurrence of pesticide poisonings[4] in the tobacco growing areas has been made.
In Brazil, there is a general lack of official data; also lacking are precise statistics for pesticide poisonings and deaths for the country as a whole. The Health Secretary of Paraná reported 9,540 officially registrated cases of pesticide poisonings from 1986 to 1997 in this state. Almost 10% (919 cases) resulted in death. Of all reported cases 23% were attempted suicides. It is not clear what percentage of the cases of poisoning involved tobacco growers.

As in many other countries (Jeyaratnam, 1987; Hettiarachchi, 1989; Wesseling, 1993; Fernando, 1995; Keifer, 1996), the official numbers of pesticide poisonings in Brazil are highly under-reported. The World Health Organization estimates that there are 50 cases of poisoning for every case reported (PANNA, 1997). This can be explained by several factors: people do not seek help from a medical doctor, cases of poisoning are misdiagnosed (for instance food intoxication), and doctors and health workers often do not report cases of pesticide poisonings. According to the Ministry of Health in Brazil, 6,000 cases of pesticide poisoning were reported in 1993 on a national basis (Cordeiro, 1998b). The Servico Brasileiro de Justica e Paz (SEJUP) estimates that the real number of pesticide poisonings is 300,000, and that this number rises annually (PANNA, 1997).

Pesticide poisonings can be the result of high levels of occupational or ambient exposures, or accidents involving the handling of pesticides or contaminated items. Pesticide poisoning can also be intentional as a method to commit suicide. The difference between unintentional and intentional exposure is important for this investigation. Unfortunately, registrations usually do not include this information, and when they do, misclassification is likely.

The Center for Toxicology Information reports that the main pesticides leading to poisoning incidents in the early nineties in the whole of Paraná were parathion and monocrotophos (Dinham, 1993), see table 5. Third in rank are unidentified organophosphates. Both parathion and monocrotophos are extremely toxic organophosphates. These pesticides, however, are not commonly used for tobacco cultivation in Brazil nowadays.

Tobacco farmers and union leaders themselves report that unintentional pesticide poisonings affect many tobacco farmers and community members, including children, pregnant women and the elderly (Hickey, 1997). This can be attributed to the types, amounts and application techniques of pesticides, likeliness of exposure by other exposure routes, contaminated food products, lack of awareness and training, incorrect information on labels and recent changes in pesticide labeling (Dinham, 1993). Since 1990 the Ministry of Health has changed pesticide labeling regulations. New labels for highly dangerous products resemble those for less toxic chemicals, which leads to a great deal of confusion.

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[4] A pesticide poisoning is officially defined as the occurrence of damage or disturbance caused by a pesticide and includes intoxication (FAO, 1990B).

It is quite possible that the high rates of pesticide poisoning leads to an elevated occurrence of depressive disorders and related suicides. Unfortunately, there is no information available about the types of pesticides responsible for the poisonings or about the question of whether the group of poisoned people corresponds with the group of people with depressive disorders.

Table 5. Pesticides causing more than 10 pesticide poisoning incidents in the state of Paraná in 1990 and part of 1991 (*source: Dinham, 1993*)

Pesticide	1990	part of 1991
2,4D+picloram	19	-
chlorpyrifos	14	10
deltamethrin	16	14
demeton-S-methyl	15	12
endosulfan	22	24
glyphosphate	17	10
malathion	19	-
methomyl	12	-
monocrotophos	107	76
organophosphates	55	34
paraquat	11	-
parathion	93	89
profenofos	12	17

Chapter 7 THE VARIOUS STAGES OF TOBACCO FARMING

All commercial tobacco plants are grown in a seedbed and later transplanted to the field. Each variety has its own specifications in spacing, pest control, time and specific crop management. Growing tobacco is labor-intensive. Per hectare it takes 3,000 hours of labor. Growing maize, for instance, takes only 265 hours of labor. This chapter describes the general practices of tobacco cultivation and is based on several authors (Garner, 1951; USDA, 1976; Akehurst, 1981, D'Hallewin, 1992).

The Brazilian tobacco season starts in August and ends in January. The harvesting season lasts from November to January. Most Brazilian tobacco farmers do not have access to modern techniques. Most work is done by hand and oxen.

Seeding

After the seedbed or plant bed has been prepared, the pregerminated tiny seed is planted by hand and raised carefully. Successful tobacco culture depends on a good supply of well-developed, healthy seedlings. A special cotton or plastic cloth is spread out over the seed bed by wires, poles or strings placed across a frame surrounding the seedbed. The cloth helps to protect the seedlings from cold and insects and reduces soil drying.
Tobacco seedlings grow flat on the ground and begin to elongate when they have about four to six leaves. As soon as the seedlings begin to elongate the cover is removed and replaced at a higher level.
In flue-cured tobacco a straw bed is sometimes used. The bed is made by spreading a thin coat of clean wheat, oat straw or pine needles over the bed area. The cloth cover is placed directly over the straw.

In this stage, the control of weeds, diseases, nematodes and insects is very important. Hand weeding can destroy the tobacco seedlings. Methyl bromide gas is widely used for seedbed treatment, both before and after seeding. It controls most soil-borne diseases, weeds and nematodes, and it provides temporary control of many soil pests. Steam and other pesticides are also used to control weeds, soil fungi, nematodes and insects.
The seedlings are watched closely to determine the need for water and fertilizer. Protection from extremely cold temperatures is provided by extra covers.

Where permanent seedbeds are used, rotation crops are common. Farmers plant small grains and legumes, such as soybeans and velvet beans, that are resistant to nematodes.

Field preparation

Land preparation involves weed control and loosening the soil. Transplanting has a better chance of succeeding if the soil is fine enough to flow back around the roots. These requirements are also similar for direct seeding in the fields.

The following mineral nutrition and fertilizers are added: nitrogen, phosphate, potassium oxide, calcium oxide, magnesium oxide, copper sulfide and zinc sulfate.

Concentrations are based on soil analyses. Placement is done in a double or single band in the ridge, in the planting hole, in one or two dollops in holes at the side of the planting station, in a circle buried a little below the surface around the plant, or more deeply at 25-40 cm.

Transplanting and cultivation

The strongest seedlings are used for planting in the field. At the time of transplanting they have four to six fair-sized leaves and are 5 to 6 inches high. The usual time of transplanting differs for the various types of tobacco. Moisture levels at the time of planting are critical for the establishment of the crop. The crop is planted by hand in a row and at a fixed distance with a density of 15,000 to 18,000 plants per hectare. For the sake of uniformity, gaps are refilled within one week and weak plants are replaced two to three weeks after planting. Cultivation primarily involves weed control and soil aeration when the soil is compacted by heavy rains.
Within the country growing and climatic conditions vary, resulting in different tastes and appearances of tobaccos of the same type.

During the growing process pests (including pathogens and weeds) are controlled by the use of many kinds of pesticides. Since the harvested product is the leaf itself, a high degree of control is aimed at leaf-attacking pests.

Topping and suckering

To promote leaf development flowers and suckers are removed as early as possible, approximately after 8 weeks in the field. This 'topping' also promotes the biosynthesis of aromatic compounds and other essential chemical compounds.
For Burley and Maryland tobaccos, the tops are broken off by hand when the plants begin to flower or when the plants have reached full flower about 2 or 3 weeks before harvesting. For flue-cured tobacco, the tops are removed at early to medium flower, about the time harvesting begins. For fire-cured, ark air-cured and cigar-filled types, the plants may be topped as soon as they have sufficient leaves and before flowering. The number of leaves left on the plants and stalks partially depends on the type of plant and weather conditions.
After the plant has been topped, suckers develop in the leaf axils and should be removed or controlled once or twice. To break the suckers off by hand is a time-consuming and laborious operation. Maleic hydrazide, a systemic growth regulator, is widely used. Contact growth regulators include fatty alcohols and certain light mineral oils.

Harvesting

Leaves are harvested by hand at intervals of approximately one week. For leaf cutting varieties this is a continuous activity as the leaves ripen upwards from the base of the plant. It involves removing a few leaves and leaving the stalk and other leaves intact. For stalk cutting varieties all plants in a field are cut at the same time. They are left in the field for a few days to wilt. The leaves are removed from the stalk after having been cured.

Curing

Different varieties of tobacco are cured in different ways. In southern Brazil, the main varieties are flue-cured (or Virginia) types. These are picked when green and dried in a heated building called a barn. Wood is grown on farms (approximately 30% of the farm land) for fuel and is used to provide the heat that is circulated through the barn in pipes or flues. The curing occurs under strictly controlled temperature and humidity regimes to ensure that the chemical changes proceed to a desired point. Practically all starch changes to sugar. Curing takes 6 to 8 days. After having been cured the leaf is bright lemon, orange or mahogany.
Another variety of tobacco, Burley, is also widely grown in Brazil. This variety is air-dried. Many popular brands of cigarettes are blends of flue-cured and burley tobaccos. Two other types of tobacco are fire-cured and sun-cured. For fire-cured tobacco heat is supplied by open smoldering fires to give the product a smoked aroma and flavor. Sun-curing techniques are used mainly in oriental tobaccos. A strong flavor and taste is developed in the first phase of curing and then retained by drying leaves outside in the sun.

Grading

Grading is the sorting of leaves into uniform lots according to body, color and degree of blemish or damage. The resulting lots are classified according to general appearance and are then ready for transport.

Chapter 8 EXPOSURE TO PESTICIDES RESULTING FROM TOBACCO CULTIVATION IN PARANÁ

Types of pesticides used in tobacco farming

Pesticide application is intensive in several periods of tobacco cultivation: seeding, field preparation, after planting and during harvesting. The types and amounts of pesticides used in tobacco cultivation differ worldwide due to differences in climate, pests, varieties, etc. (Rich, 1989; Drake, 1998). In only very few countries do governments actually control what tobacco producers use in the field. In 1992 the US Environmental Protection Agency (EPA) conducted a survey of pesticides registered for use on tobacco crops worldwide (Drake, 1998). The Brazilian government officially registrated the following list for use on the tobacco crop: methylbromide, dazomet, decamethrin, acephate, endosulfan, methaldeid, fenthion, carbaryl, diazinon, carbofuran, permethrin, fatty alcohol, and thiabendazole.

Pesticides officially registered for use on tobacco, however, are very often the opposite of what is actually used on tobacco (Drake, 1998). Therefore this information from the Brazilian government will not be used as the only source of information for the evaluation of exposure to pesticides. Other sources are the Catalog of Agrochemicals of Andrei (1996), the Tobacco Growers' Association of Brazil AFUBRA (1998) and the tobacco company Souza Cruz (1993).

A list of the most important pesticides used in tobacco cultivation in Brazil is presented in table 6. Pesticide prescriptions on farms, newsletter articles and AS-PTA (a Brazilian non-governmental organization) indeed report on many pesticides present on this list. Almost 50% (13 out of 27) of the pesticides in this list have a possible causal relation with depressive disorders. Some of the neurotoxic pesticides are discussed in more detail. Sources are Extoxnet, Hayes (1991), Tomlin (1994) and Hickey (1998).

aldicarb (Temik) - Aldicarb is a extremely toxic carbamate insecticide. It is acutely toxic and can cause chronic damage to the nervous system. Furthermore, it suppresses the immune system and adversely affects the fetus. It is banned in at least 13 countries, but still widely used in tobacco. It has been found in the groundwater of 27 states of the United States of America.

chlorpyrifos (Lorsban 480 BR) - Chlorpyrifos is a widely-used organophosphate insectide. It is highly toxic and poisonings are reported very often. Symptoms of acute poisoning include headache, nausea, muscle twitching and convulsions. It is easily to affect the central nervous system. Furthermore, it affects the reproductive system and causes genetic damage and birth defects. Chlorpyrifos is known to contaminate the air, groundwater, surface waters, rainwater and fog, with residues being found up to 20 kilometers from the site of application.

Table 6. The most important pesticides used in tobacco cultivation in Brazil *(sources: Andrei, 1996; AFUBRA, 1997)*

Commercial name	Chemical name	Group	Type	Possible relation with depression*	Toxicity **
Sevin 7,5; Carvin	carbaryl	carbamate	I	yes	Moderate
Acefato Fersol 750 PS	acephate	organophosphate	I/A	yes	Moderate
Orthene 750 BR	acephate	organophosphate	I/A	yes	Moderate
Doser	n.a.	organophosphate	I	yes	Highly
Confidor 700 GRDA	imidachlorprid	chlornicotinyl	I	yes	Slightly
Lorsban 480 BR	chlorpyrifos	organophosphate	I	yes	Highly
Solvirex	disulfoton	organophosphate	I/A	yes	Extremely
Furadan	carbofuran	carbamate	I/N	yes	Extremely
Temik	aldicarb	carbamate	I/N/A	yes	Extremely
Brometo de Metila	methyl bromide	alifate	F	yes	Extremely
Basamid G	tiadiazine	fumigant	F	n.a.	Moderate
Dithane PM	maneb?	dithiocarbamate	F	yes	Moderate
Manzate 800 PM	mancozeb	dithiocarbamate	F	yes	Moderate
Tecto 600	thiabendazole	benzimidazole	F	no	Slightly
Rovral	iprodione	dicarboxymade	F	no	Slightly
Cobre Sandoz BR	n.a.	n.a.	F/B	n.a.	Slightly
Ridomil 50 GR	metalaxyl	alaninate	F	no	Slightly
Primeplus	flumetraline	n.a.	GR	n.a.	Highly
Antak	n.a.	n.a.	GR	n.a.	Moderate
Devrinol 500 PM	napropamide	amide	H	no	Moderate
Gamit	isoxazolidinovas	n.a.	H	n.a.	Highly
Herbadox 500 CE	pendimethalin	dinitroaniline	H	no	Highly
Fusilade 125	fluazifop-p-butyl	aryloxifenoxypropionate	H	no	Highly
Poast	sethoxydim	hydroxycyclohexane	H	no	Highly
Assist	mineral oil	n.a.	n.a.	n.a.	Slightly
Lesmix	methaldehyde	n.a.	n.a.	n.a.	Moderate
Formicida Mirex	sulfluramide	organochloride	I	yes	Slightly

*Possibility of a relation with depression and suicide. Based on the toxicological information in chapter 4.
**Toxicity based on the official Brazilian classification of pesticides, largely corresponding with the WHO Classification of pesticide toxicity.
A=acaricide; F=fungicide; GR=growth regulator; I=insecticide; N=nematocide
n.a.=not available

acephate (Orthene, Cefanol) - Acephate is an organophosphate foliar spray insecticide of slight toxicity and moderate persistence. It is considered a General Use Pesticide and can be found in a variety of commercial products. Exposure to acephate can have several effects in humans, including central nervous system impairments and reproductive effects.

methamidophos (Tamaron) - Methamidophos is extremely toxic and registered as a Restricted Use Pesticide. It is an organophosphate insecticide and a potent acetylcholinesterase inhibitor. It is highly toxic to mammals, birds and bees, and can cause neurological, reproductive, teratogenic and mutagenic effects. Because it is rapidly absorbed through the stomach, lungs and skin, special personal safety equipment is required for its application.

mancozeb (Dithane, Manzate) - Mancozeb itself is a practically nontoxic ethylene bisdithiocarbamate used in many crops to protect against fungicides, commonly in combination with zineb and maneb. Mancozeb is registered as a General Use

Pesticide. Mancozeb is rapidly absorbed into the body from the gastrointestinal tract. Occupational exposure can cause sensitization rashes. The major metabolite of mancozeb, ethylene thiourea (ETU), however, is carcinogenic and of toxicological significance.

disulfoton (Solvirex 50, Solvirex 100) - A highly toxic organophosphate, inhibiting cholinesterase and affecting the functioning of the nervous system. All products formulated at more than 2% disulfoton are classified as Restricted Use Pesticides. They may be purchased and used only by certified applicators. The compound is highly toxic to mammals by all routes of exposure. It might cause reproductive, teratogenic, and mutagenic effects.

methylbromide (Brometo de Metila) - Methyl bromide is a highly toxic compound, registered as a Restricted Use Pesticide. It is widely used as a gas soil fumigant against insects, termites, rodents, weeds, nematodes and soil-born diseases in a wide variety of crops. The most important route of exposure is by inhalation, and it can be highly irritating to the skin and respiratory system. A delay in the onset of symptoms following exposure and an odor threshold well-above the level at which toxic effects occur lead to many human poisoning incidents. Furthermore it can cause neurological damage and mutagenic and carcinogenic effects.
Another important factor is that the application of methyl bromide leads to ozone depletion. At the moment of writing discussions about banning this compound are in progress.

carbofuran (Furadan) - Carbofuran is a broad spectrum carbamate pesticide used against insects, mites and nematodes. Formulations are highly toxic or moderately toxic. Granular formulations are classified as Restricted Use Pesticide because of their toxicity to birds. Liquid formulations are classified as Restricted Use Pesticides as well because of their acute oral and inhalation toxicity to humans. Carbofuran is poorly absorbed through the skin. The most important toxic effects are neurological.

imidaclorprid (Confidor 700 GrDA) - Imidaclorprid is a relatively new chloronicotinyl pesticide used against insects. Like nicotine it mimics acetylcholine, blocking the postsynaptic nicotinergic acetylcholine receptors, but is less toxic to humans than nicotine. Imidaclorprid is of moderate toxicity. It is absorbed quickly by the gastro-intestinal tract.

Application practices

An indication of the amounts of pesticides used in tobacco and the application techniques are given in table 7. The amounts are based on a pesticide instruction board present at a tobacco farm in Paraná in 1997. In practice, application of pesticides varies from 30 to 100 kilogram per hectare, depending on diseases, climatical conditions, etc.

Some pesticides are applied in a fixed frequency or after rainfall, others are applied every time there is a plague. The duration of the application for the farmer depends on the stage of plant growth and size of the tobacco plot. Spraying sessions mentioned in a Malaysian tobacco study (Cornwall, 1995) lasted from 20 minutes to 5 hours. Times

for mixing, loading and cleaning are not known.

Table 7. Amounts of pesticides and application techniques in tobacco cultivation according to a pesticide application board on a tobacco farm, 1997.

Seed bed					
Trade name	Chemical name	Concentration in water	Application	Quant. p. seed bed	Frequency
Orthene/Cefanol	acephate	0.667 g/l small seedlings 1.333 g/l big seedlings	backpack	15 liter 15 liter	every time when there is a plague
Confidor 700 GrDA	imidachlorprid	0.063 g/l	watering can	160 liter	Before seeding and 15-20 days before transplanting
Dithane/Manzate	mancozeb	0.667 g/l small seedlings 1.333 g/l big seedlings	backpack	15 liter 15 liter	every 7 days or after rainfall
Rovral	iprodion	0.031 g/l (or 0.062 g/l.)	watering can	160 liter	every 7 days or after rainfall
Field					
Trade name	Chemical name	Concentration in water	Application	Quant. p. 1000 plants	Frequency
Orthene/Cefanol	acephate	5.0 g/l	backpack	10 liter	day of planting and when pests are present
Doser 300	n.a.	4.2 g/l greenhouse 3.5 g/l barn	backpack	15 liter 15 liter	Day of planting and 15-20 days later (without Solvirex)
Solvirex	disulfoton	100%	with fertilizer	1 kg	
Prime plus	flumetralin	10.4 g/l greenhouse 5.3 g/l barn	backpack	15 liter 15 liter	After cutting, till 2.5 cm
Confidor 700 GrDA	imidachlorprid	2 g/l greenhouse 2 g/l barn	backpack	15 liter 15 liter	Directly after planting

n.a.=not available

Pesticides are applied using a 15-liter backpack or a 40-liter watering can. Since tobacco is a rapidly growing tall row crop and spraying in the field occurs from a deep narrow ditch, exposure of workers to pesticides at this stage is inevitable. Personal safety equipment such as gloves, a mouth and nose cover or a head cover are hardly used (Ten Hoeve, 1999). No information is available about other factors, such as the performance of recommended re-entry times, training and education, personal hygiene, and the state of equipment.

Unfortunately, since no occupational exposure studies for tobacco farmers in Paraná have been done and field measurements were beyond the scope of the project, no data are available on occupational exposure levels.

Chapter 9 OTHER ROUTES OF EXPOSURE TO PESTICIDES

In addition to the occupational exposure of farmers to pesticides during tobacco farming activities, there are also other ways in which people can come into contact with pesticides. People can use pesticides in their home environment and in other occupational activities. Moreover, since farm communities have their houses close to their agricultural activities, pesticide contamination in and around the home is likely to occur. The last exposure route considered here is the pesticide contamination of food products.

Domestic use

Pesticides are not only used in agriculture but are also applied for mosquito prevention (in the fight against malaria and dengue), the elimination of insects, rodents and other vermin, and for weed control around the house. Pesticides are applied inside or around the house. Especially inside the house does pesticide degradation take longer (Anderson, 1988; Lewis, 1994; Whitmore, 1994) and there is a reasonable chance of ambient exposure to pesticides.
When pesticides are easily available at the farm, it is quite possible that these chemicals will be applied domestically as well.

Use in other occupational activities

Most tobacco farmers in southern Brazil use only part of their land (11.6%) for tobacco cultivation. Approximately 30% of the land is covered with forests for fuel for the curing process. Approximately 23% is used for parallel crops such as maize, black beans or onions (ITGA, 1997). The percentage of crop rotation after tobacco is 79.9%, and usually involves maize (AFUBRA, 1997). It could be possible that pesticides are also used in these crops.

Ambient exposure

Only a small amount of the chemicals used in any applied pesticide reaches its target organism. Up to 85 to 90 percent of the applied pesticides are removed from the application site by rain, wind (drift), evaporation, and other agents (Moses, 1993). In general, pesticides can move through air, water, and soil. Because tobacco farming families live at short distance from agricultural fields where pesticides are used, contamination of their ambient environment (both inside and outside the house) is likely to occur (Brown, 1993; Whitmore, 1994; Beard, 1995; de Cock, 1995; Simcox, 1995; Smits, 1999). Exposure may be possible by dermal absorption, inhalation or oral uptake from air, surface water, drinking water, and soil. Acute poisonings and accidents in developing countries have been reported to have occured, for instance by the breathing of pesticide drift from nearby crops and drinking from contaminated waterways (Utsch, 1991; Wesseling, 1993).
Indirect factors can also contribute to non-occupational contact with pesticides Examples of such factors are the handling and use of contaminated materials such as empty pesticide containers, the storing of pesticides near or inside the house, the transportation of pesticides, and the washing of contaminated work clothes (Wesseling, 1993).

There is not much information available about the environmental contamination of surface water, groundwater, air and soil.
The Toxicology Center of the University of Sao Paulo State investigated irrigation water and drinking water. In 35.3% of the water samples they found organophosphate and pyrethroid residues at levels above World Health Organization standards (Inoue, 1993).
An older study on chlorinated pesticide residues in the domestic water supplies of the cities of São Carlos and Araraquara revealed the presence of BHC, DDT, endosulfan and chlordane. Concentrations were below the permitted standards set by Brazilian legislation (Caceres, 1981).
The state of Paraná is one of the main agricultural regions of Brazil. Paraná is Brazil's biggest producer of cotton, cacao, beans, corn and wheat. The largest numbers of pesticides in all of Brazil are applied here (Knight, 1997). The few studies on pesticide residues in the environment do not provide enough evidence for severe environmental contamination. However, taking other studies on environmental contamination and intensive pesticide use into consideration, it cannot be denied that direct ambient exposure to pesticides is likely to be the case in Paraná as well.

However, indirect factors also play a role in the exposure of tobacco farmers to pesticides. Experts estimate that 14 million bags, bottles and plastic containers that once held pesticides are scattered throughout Brazil. In rural areas, these containers are often reused as pans, cups or water containers, and children are frequently found using them as toys (Hickey, 1998).
A few years ago tobacco companies made a commitment to collect empty pesticide cans and bottles in Paraná. Nowadays, farmers have hundreds of empty cans and bottles stored on their farms, but the companies fail to collect them (PANNA, 1998).

Residues in food

Pesticide residues in food can contribute proportionally to the total amount of pesticide intake. Residue levels on the outside of the product can be high when the time between pesticide application and food consumption is too short for the pesticides to degrade and when pesticides have not been washed off properly. Persistent pesticides can also end up in a crop due to cultivation with contaminated ground water, or they can find their way into living tissues where they can bioaccumulate up the food chain into human diets (Repetto and Baliga, 1996).

There is no routine control of food products. Only a few studies of pesticide residues in food are carried out in Brazil. Spot check tests from farmers' markets in several cities in the early nineties suggested that 2-5% of the food contains residues in excess of legal limits established by the Brazilian government and/or Codex Alimentarius, an UN body which sets limits (Dinham, 1993).
A more comprehensive study was carried out by the Instituto de Tecnologia de Alimentos in 1981-1982. For two years 49 different widely-consumed processed food products were purchased monthly in São Paulo supermarkets. Of the 1176 samples, 41% contained residues surpassing official limits. Of the 49 products 11 had illegal residues in minimally 80% of their samples. All the samples of two different brands of soy oil were contaminated.
A study of concentrations of agrochemicals in food and water in the municipalities of

Pederneiras, Macatuba and Lencois Paulista by the University of Sao Paulo State found organophosphate and pyrethroid residues at levels above World Health Organization standards in 11.1% of the investigated food products (Inoue, 1993). Sometimes products are found contaminated with restricted pesticides. In 1989 Paraná State Inspectors confiscated tons of apples contaminated with dicofol, a pesticide banned since November 1985 (Dinham, 1993).
Because of the intensive use of pesticides in tomato crops, a study was carried out in 1999 on the contamination of the final product. Residues were found from insecticides and fungicides used during the frutification and maturation stages; these residues included captan, chlorotanolil, cyhalothrin and copper (Segura Zavatti, 1999).

These incidental studies give reason to believe that Brazilian food products are frequently contaminated with hazardous pesticides, including organophosphates. This includes products such as soy products and fruit that are consumed frequently by farmers in the south of Brazil. However, with regard to the tobacco study there is not enough information to assess the contribution of organophosphate intake due to residues on food. When carrying out a risk assessment, however, this possible exposure route has to be taken into account.

Conclusions

Domestic use, other farming activities, ambient exposure and residues in food are all likely to contribute to the chronic exposure of tobacco farmers to pesticides in Paraná. Some of these exposures, such as ambient exposure and domestic use, can be indirectly related to tobacco farming and other agricultural activities and to the easy availability of pesticides. However, data on these non-occupational exposures are insufficient to determine their impact.

Acute high exposure

Unintentional pesticide poisonings affect many tobacco farmers in Paraná, both occupational and non-occupational. Among the pesticides frequently causing these poisoning incidents are the group of organophosphates. Toxicological and epidemiological studies point out that it is very quite possible that organophosphates have a causal relationship with depressive disorders. Therefore, cases of organophosphate poisoning might be an important group of people at risk.

Chronic low exposure

Because no hard evidence or threshold limits exist for pesticides and their relation to depressive disorders, and because of the absence of information on levels of exposure to pesticides during tobacco farming in Paraná, no proper risk assessment for chronic low exposure can be realized.
Of the 27 most important pesticides used in tobacco cultivation, almost half is likely to have a causal relationship to depressive disorders. There is only one field study which assesses the level of exposure to pesticides during tobacco cultivation (Lonsway, 1997). It was executed in Kentucky, in the USA in 1994 and 1995. Dermal and respiratory exposures were measured from acephate, the acephate metabolite methamidophos and endosulfan. Table 8 gives an overview of the results of this study. Exposures do not exceed safety limits, but caution is advised.

Table 8. Exposure of mixers/sprayers to insecticides applied to tobacco in Kentucky in 1994 and 1995, from a study by Lonsway et al. (1997)

exposure data		Dermal mg/kg/d	respiratory mg/kg/d	PTDPH* %	MOE**
acephate	Mixing	5.13	0	0.030	59
	Spraying	0.24	0	0.002	1250
methamidophos	mixing	0.26	0.01	0.085	56
	spraying	0.54	0.04	0.302	21
endosulfan	mixing	16.18	0.01	0.541	1843
	spraying	8.06	0	0.413	3722

*PTDPH percentage of toxic dose per hr
**MOE margin of exposure (insecticide NOAEL value divided by 10% of dermal plus 100% respiratory exposure amounts). A small MOE indicates an exposure close to the threshold level, and a large MOE indicates an exposure far below the threshold level.

Exposure is always influenced by many factors. It can differ per pesticide, production stage, application techniques, ventilation circumstances, meteorological conditions, work practices and personal protections devices (Boleij, 1995). It is known that Brazilian application techniques and work practices differ greatly from those in Kentucky. An important difference, for instance, is the use of a tractor-mounted boom sprayer and an open-air highboy versus the use of backpack sprayers and watering cans. Therefore, it is not possible to simply extrapolate these data to the Brazilian situation. Based on these data the possibility that limits of exposure are exceeded in Brazil cannot be excluded. To make a more appropriate assessment of the occupational exposure of tobacco farmers to pesticides in Paraná, an exposure study should be conducted with personal measurements in the field.

Non-occupational exposure

In a total risk assessment other non-occupational exposures should be taken into account too. Domestic use of pesticides, other farming activities, ambient exposure and residues in food are all likely to contribute to the chronic exposure of tobacco farmers to pesticides in Paraná and to a higher pesticide burden. Some of these exposures are indirectly related to tobacco farming and other agricultural activities and to the easy availability of pesticides.

Other risk factors for depression and suicide

In addition to the risk of exposure to pesticides other risk factors for depression and suicide are also present in the lives of the Brazilian tobacco farmers. The most important ones are financial problems, a strong dependency on the tobacco industry, the easy availability of toxic substances and the publicity given to acts of suicide. However, it is not possible to quantify this information and to assess the actual impact of these factors.

Chapter 11 CONCLUSION AND RECOMMENDATIONS

Conclusion

The aim of this pilot study was to assess the possibility of a causal relationship between the use of certain pesticides in tobacco cultivation in Brazil and the occurrence of elevated levels of depression and suicide. The results of this study are not based on either field observations or measurements; in fact, many assumptions have had to be made. But the available information suggests that *such a causal relationship, although not proven, may indeed exist.*

Recommendations to minimize exposure

In view of the scope of this study, it is not possible to give specific practical recommendations to minimize exposure to pesticides which are directed at the situation among tobacco farmers in Paraná, Brazil. The aims of the recommendations described below are 1) to minimize the occupational exposure of tobacco farmers to pesticides which are suspected of causing depression and suicide; 2) to decrease the number of unintended poisonings with these pesticides; and 3) to minimize non-occupational exposure to these pesticides by environmental contamination and pesticide residues on food.

With regard to these aims, research on the following pesticides used in tobacco cultivation should focus on:
Sevin 7,5 and Carvin (carbaryl), Acefate Fersol 750 PS (acephate), Orthene 750 BR (acephate), Doser, Confidor 700 GRDA (imidachlorprid), Lorsban 480 BR (chlorpyrifos), Solvirex (disulfoton), Furadan (carbofuran), Temik (aldicarb), Brometo de Metila (methyl bromide), Dithane PM (maneb), Manzate 800 PM (mancozeb), and Formicida Mirex (sulfluramide).

General advice can be given by following the general FAO Guidelines on 'Good Practice for Ground and Aerial Application of Pesticides' (1988) and the FAO Guidelines for 'Personal Protection when Working with Pesticides in Tropical Climates' (1990a).
At the level of the individual, the proper use of personal safety equipment and the improvement of work practices and equipment can be achieved by, for instance, training and education. Special attention should be paid to exposure to pesticides during the mixing and loading of pesticides, safe storage and the proper disposal of empty pesticide containers.
A system of Integrated Pest Management should also be implemented (FAO, 1988). This is a pest management system that, in the context of the associated environment and the population dynamics of the pest species, utilizes all suitable techniques and methods in as compatible a manner as possible, maintaining the pest population at levels below those causing economically unacceptable damage or loss. When natural control fails, other important available methods are:
-cultural control: modifying cultivation practices, removing host plants, crop rotation, modifying of planting dates;
-mechanical control: hand weeding, light traps;

-physical control: hot water treatment;
-biological control: using natural enemies to control pests by either releasing these into the environment or allowing natural dissemination;
-chemical control: proper application of pesticides.
Furthermore, at a higher level, improved legislation and maintenance of regulations should play an important role in minimizing exposure to pesticides at the workplace, at home and on food residues.

Remarks on other risk factors for depression and suicides

Disposition to depression and related suicide is a very complex item. Besides chemicals, many other social and psychiatric factors can play a role. The problem of high depression and suicide rates among tobacco farmers in Paraná should be regarded in its largest context. Some factors are strongly present in the farmers' lives, such as a strong dependency on the tobacco industry, financial problems, the easy availability of toxic substances and the publicity given to acts of suicide.
These factors should not be forgotten when working on reducing the rates of depression and suicide among tobacco farmers in Paraná.

Recommendations on further research

The results of this research are mostly based on general information, and a set of assumptions had to be made. To be able to draw more fundamental conclusions specific to the practical situation among tobacco farmers in Paraná, Brazil, the following scientific studies are recommended:
-toxicological research to gain more knowledge on the relation between pesticides and depression and suicide, including mechanisms, threshold levels and effect modificators;
-epidemiological studies to gain insight into the rates of depression and suicides among tobacco farmers in the state of Paraná and other tobacco states in Brazil compared to other farmers and the mean population;
-research to gain insight into other risk factors on depression and suicide, such as social-economic, psychological and chemical factors;
-epidemiological research on exposure to pesticides and depression and suicides among tobacco farmers in Brazil to gain more insight into the actual causal relationship. This could be achieved, for instance, by a cohort study including field measurements to determine the occupational and non-occupational exposure of tobacco farmers to pesticides which are able to cause depressive disorders, measurements of both acute high level and chronic low level exposure, and measurements of affect from, for instance, neuropsychological tests. Another study could involve a case-control study, in which the exposure to pesticides among a group of depressed individuals is assessed compared to the exposure among a group of non-depressed people;
-research to formulate control measures to lessen the risk of tobacco farmers in Paraná at the individual, industrial and state level.

In November 1999 a comprehensive epidemiological study on health, environment, and socio-economical problems among tobacco farmers is going to be started in Rio Grande do Sul. In line with the objectives of the Global Ministries the Netherlands, it is advisable to pay attention to the results of this research. Final results are expected in August 2001.

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