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Effects of Pesticides and of Nitrate and N-nitrosocompounds on Human and Animal Health in the Tropics: Epidemiological and Toxicological Aspects (**)

It is surprising that whereas the U.S.A. is using more than one-third of the whole production of pesticides, much fewer accidents per year than in tropical countries are recorded.

An analysis of the problems in tropical countries shows that toxicological parameters are different for various reasons.

First, the spectrum of insecticides changes considerably from one country to the other, depending on specific requirements.

Second, the regulations for the use of pesticides also differ from one country to another, being generally looser than in, e.g., U.S.A. or western Europe.

Third, a pesticide elaborated in a definite socio-cultural context acquires quite different implications when this context is modified, sometimes drastically. A fourth point should be borne in mind: the general ignorance of the real dangers of poisoning. The toxicology of pesticides should take into account acute effects as well as long-term effects comprising teratogenic, carcinogenic and mutagenic effects.

For obvious reasons, acute poisonings, either accidental or voluntary, are more often recorded. Epidemiological evaluations are difficult, however, since from the proportion of deaths recorded in a finite population, it is not easy to derive the proportion of contaminated persons, the degree of contamination, and to what extent the epidemic will spread.

Now *a priori*, in considering only toxicology and epidemiology of acute poisoning, we are neglecting potential long-term effects.

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Unfortunately, the evaluation of such complex effects can only be extrapolated from data which should ideally include, not only the bulk of our knowledge on animal experiments, but also the specific use or misuse of the pesticide in the country under investigation.

In various textbooks, the large number of pesticides available today are classified in different ways. First, according to their use as insecticides, herbicides, fungicides, molluscicides, rodenticides and nematocides, i.e., by the name of the organisms to be eradicated.

Second, inside each group, they can be classified by their chemical formula. Since the chemical properties of the molecules will determine their pharmacological and ecological properties, this is certainly the best way to get information about the structure-activity relationships from which recommendations for skilful use can be derived. There is an alternative way to proceed. It is to elaborate a practical classification based on the hazards which take into account the toxic properties and the distribution and use of each pesticide. WHO attempted to develop such a classification, which was adopted in several developing countries and by the Council of Europe in 1977. (WHO/FAO 1979; Plestina, 1984). In this classification, about 500 pesticides were classified according to a single L.D. 50 dose — L.D. 50 is certainly not the best way to describe and to predict toxicity. Moreover, this classification takes into account only acute risks and not potential long-term hazards. However, this effort to get a practical and efficient classification was rewarding.

In the present context, it is out of the question to review exhaustively the toxicology of pesticides enumerated in this classification. We rather aim to identify in each classical category problems raised by the most frequently used pesticides in tropical countries.

In tables 1, 2, 3, 5, 7, 8, we attempt to incorporate some data involved in WHO's classification.

TABLE 1 - Classification of some OPI's used in tropical countries.

Name	LD50 oral	in rat dermal	WHO classif.	Risks
Parathion-ethyl	3.6	6.8	IA	++++
Parathion-methyl	14	67	IA	++++
Leptophos(phosvel)	43	800 (rabbit)	IA	++++
Dichlorvos	56	75	IB	+++
Trichlorfon *	560	—	III	+++
Dimethoate	c 50	353	II	++
Malathion	1,000	4,444	III	+++

* Used also as anthelmintic.

TABLE 2 - Classification of some OCT's used in tropical countries.

Name	LD50 oral	In rat dermal	WHO classif.	Risks
Aldrin	18.50	98	IB	+++
Dieldrin	46	600-900	IA	++++
Endrin	7.5	15	IB	+++
DDT and derivatives	250	250,500 (oil) 2,510 (powder)	II	++
Lindane	88-225	900	II	++
Heptachlor	100	195	195	++
Hexachlorobenzene HCH	100	—	II	+++

A. INSECTICIDES

1. *Organophosphorus Insecticides (OPI)*

Chemical and biochemical properties of organophosphorus insecticides have been amply described since the last World War.

It is important to schedule first some points of interest to understand the toxicology and epidemiology of such widespread compounds. They are highly reactional compounds easily biodegraded. From their phosphorylating activity, we can derive short-term effects whereas from their alkylating properties we can infer potential long-term effects (survey in Moutschen *et al.*, 1984).

The phosphorylation processes, namely the preferential attack of the phosphorus atom followed by the cleavage of the P-O bond results in the inactivation of acetylcholinesterase. The inactivation of this enzymatic system can explain by itself the main toxic effects to sensitive organisms, i.e., the acute toxicity. The insecticidal properties of organophosphorus compounds are obviously due to the inhibition of acetylcholinesterase at the endings of the nerves.

They are clearly nervous poisons. The rationale for using such compounds as powerful insecticides is that in insects, acetylcholine acts predominantly as a transmitter in the synapses of the central nervous system, but not the peripheral nerves. In mammals, the cholinergic symptoms induced by organophosphorus compounds can be subdivided in two stages, as is the case of most nervous poisons: an initial stimulation of cholinergic transmission, characterized by convulsion, followed by, among other symptoms, a depression leading to paralysis especially of the respiratory system.

Epidemiologic studies of such acute poisonings have been carefully described. Although industrialised countries are generally dealing with occupational hazards

in the factories in which such compounds are prepared, the development of events after poisonings is not at all the same in tropical countries. The example of Tunisia shed light on some problems. In this country, as in others, one of the most powerful organophosphorus compounds is given free, and only in 1980, 140 tons of this insecticide were sold. In a 5-year period, from 1975 to 1980, 1132 cases of acute poisonings attributed to this drug were hospitalized, which might still be an underestimation of the total cases of acute poisonings.

An analysis of these cases revealed that a large proportion of them (89%) were suicides. Parathion was taken as its commercial formulation (Yacoub *et al.*, 1981). In this specific case, most patients could be saved by an equipped « center » which took care mainly of urban cases, but the situation could be worse if we consider rural regions.

There are a lot of other examples of epidemiological studies due to organophosphorus compounds. Phosvel (leptophos) is a special OPI, the symptoms of which are delayed, appearing only 8-13 days after exposure. A large amount (1.5 tons) was used in tropical areas in 30 different countries. We should mention epidemics of acute poisonings especially in Egypt, where it was most investigated, and also in Colombia (1977-1978), Costa Rica, Indonesia (1980) and Nigeria (1983) (Shea, 1977).

In spite of its relatively low toxicity, malathion was responsible for important epidemics. In Guiana, 264 cases of suicides were investigated (Nalin, 1973). The toxicity of malathion was fully recognized in 1976 for malaria control in Pakistan. A number of workers (2810) were involved but only 5 deaths were reported. The knowledge of the symptoms was considerably improved (Baker, 1978 a and b).

For organophosphorus compounds, there is an example which is particular to tropical countries. It is the use of a pesticide not only as such but at the same time as anthelmintic. This is trichlorfon (metrifonate), which is not the unique example of that sort. Trichlorfon is widely used in the treatment of schistosomiasis and to a lesser extent of onchocerciasis. Dichlorvos, which is a close derivative of metrifonate, was also used for curing gastrointestinal helminthic infections of dog, pig and horse. Theoretical and practical aspects of the use of such pesticides were recently summarized (Acta Pharmacologica et Toxicologica, vol. 49, 1981).

Millions of people over the world, chiefly in tropical countries, are concerned with these two terrible pathological conditions.

It is difficult to evaluate exactly the epidemiological extension of these two diseases, but onchocerciasis alone is reported to affect 40 million people in Africa and Central America, where it comes up to 20% of the village population to be treated (Awadzi *et al.*, 1981). Now, the effects of the anthelmintic compound can be superimposed on the effects of other compounds used as insecticides in the same area.

This is a typical example of a pesticide for which intense toxicological and epidemiological investigations had to be performed, not only in short-term but also in long-term researches. Being also alkylating agents, organophosphorus

compounds are most likely candidates for long-term effects. To the best of our knowledge, no such studies were systematically undertaken in tropical countries. The sensitivity of various biological materials differs considerably.

Mutagenicity of OPI has been tested in a large variety of test systems from prokaryotes to mammals (review in Moutschen *et al.*, 1984). Some results are still controversial, however. All OPI tested so far show obvious positive effects at the chromosome level of plants. This is in itself an important conclusion for agricultural regions.

For 12 compounds which include those most often utilized in tropical countries, a structure-activity relation was established (Gilot-Delhalle *et al.*, 1983). This research includes a study of detoxification processes by liver microsomal fractions. The data suggest strongly the existence of efficient detoxification processes in man. However, it should be kept in mind that these processes depend not only on the alkylating and phosphorylating moieties of the molecule but also on the aliphatic or cyclic radicals.

From experimental genetic studies in mammals it can be concluded that OPI are not significantly clastogenic in different tissues such as bone marrow or testes. One important exception: the cases where the commercial formulation contains a combination of different insecticides for synergistic effects (Degraeve *et al.*, 1977). It raises the problem of testing the commercial formulations specifically used in different countries.

Epidemiological studies of workers acutely intoxicated with OPI (Trinh Van Bao, 1974) revealed a significant but temporary increase of chromatid breaks and stable chromosome aberrations. It was shown, however, that the level of "genetic intoxication" decreased to the control level after 6 months. The model of genetic toxicological studies is certainly Trichlorfon and Dichlorvos for the reasons mentioned above. All possible biological tests have been performed after acute, subacute and chronic treatments (Moutschen *et al.*, 1981). The data allowed to assess confidence limits for pharmaceutical use from which hazards of long-term effects could be derived. A certain number of OPI were also investigated for carcinogenicity. Here the data are sometimes difficult to interpret, and the carcinogenic effects of such compounds are not established (review in Moutschen *et al.*, 1984). In fact, the results are still conflicting and the carcinogenicity of one of the most important of them, parathion, is still questionable. Embryotoxicity was also reported but it does not seem to be a serious problem, with the exception of the cattle after repeated spraying. Trying to draw some conclusions from the bulk of toxicological and epidemiological data on OPI, it seems that long-term effects are not of great concern.

2. Organochlorine Insecticides (OCI)

Toxicological and epidemiological problems after treatments with OCI are quite different from those due to OPI. The toxicity is variable. The most frequently reported acute accidents are due to molecules such as aldrin, endrin

and dieldrin, which are cyclodienes containing a chlorine substituted endomethylene bridge. In acute intoxications such compounds induce a gastrointestinal syndrome with nausea and vomiting, sometimes associated with nervous symptoms, such as disorientation, loss of consciousness and convulsions. These latter symptoms occur in the most severe cases. In contrast with OPI, there is no specific antidote for OCI. Notorious cases of epidemics due to OCI have been reported in tropical areas. Some conclusions can be drawn.

The first factor to be taken into account is the persistence of OCI after releasing them in the environment.

The personnel involved in antipaludean campaigns, e.g., in Brazil or in India was the most widely investigated. These epidemiological studies were dealing with populations at high risks.

Results of some investigations realized under the auspices of W.H.O. (1982) are summarized in table 3.

Except some neurological signs, there was no great difference between the control and exposed groups, though in this latter one, the blood concentration of OCI was three times higher in Brazil. In India, the blood concentration, 7.5 to 15 the control concentration in exposed groups, is of the same

TABLE 3 - Total DDT in non-occupationally exposed populations.
(data from WHO, 1982)

Country	Year	N° of samples analysed	DDT mg/kg	Reference
AFRICA				
South Africa	—	—	5.9 7.2	Wasserman <i>et al.</i> (1970) Wasserman <i>et al.</i> (1970)
Kenya	—	—	5.4	Wasserman <i>et al.</i> (1972a)
Nigeria	1967	43	8.8	Wasserman <i>et al.</i> (1968)
	1969	41	6.5	Wasserman <i>et al.</i> (1972b)
Uganda	—	—	2.9	Wasserman <i>et al.</i> (1974)
SOUTH AMERICA				
Argentina	1967	37	13.2	Wasserman <i>et al.</i> (1968)
Brazil	1969-1970	38	4.1	Wasserman <i>et al.</i> (1972b)
Venezuela	1964	38	10.3	Dale (unpublished 1971)
ASIA				
India (Delhi region)	1964	67	26	Dale <i>et al.</i> (1967)
Thailand	1969-1970	77	12.6	Wasserman <i>et al.</i> (1972c)
BELGIUM				
	1965	20	3.3	Maes and Heydricks (1966)

order of magnitude as in workers who are preparing the formulation in industrialized countries.

These slight neurological signs disappeared with time, and the intensity of the symptoms could never be correlated with the blood concentration during the same period. The epidemics described above could be somewhat controlled since the spraying of OCI was programmed as a function of the extension of the paludean areas. In other cases, however, the epidemics extended in a way that resembles virus or bacterial diseases, and the origin, i.e., the hypocenter, has to be searched for. In 1967, four epidemics of poisoning arose independently in Doha (Qatar) and in Holuf (Saudi Arabia). In Doha, 490 patients were hospitalized at first, suffering from an acute gastrointestinal syndrome. The four epidemics involved 600 cases of acute poisonings resulting in 26 deaths (Jalambo, 1980). The origin of these unusual epidemics could be detected. It was proved that all patients ate bread made with a contaminated flour. The analysis of this flour, the bread and also the autopsies of deceased patients revealed the presence of an OCI: endrin. The contamination occurred on a boat on which leaking containers of endrin contaminated flour sacks located nearby. The development of such fortuitous epidemics is completely uncontrolled in contrast with those of paludean countries.

Another example of epidemiological studies after OCI was performed in Brazil, where dangerous pesticides, e.g., insecticides or defoliants, are widely used. Aldrin, another OCI with acute effects (Yorinori, 1983) was responsible for 13 deaths in the state of Para. As in the majority of epidemiological investigation, the exact extension of the area where the contaminations occurred is somewhat ill defined. It might be seriously under-estimated because of poor reporting. In fact in Brazil, 208 deaths presumably due to pesticides were reported (Yorinori, 1983).

Criteria for the control of environment polluted with DDT and derivatives have been reviewed by WHO (1982). This report led to interesting observations and recommendations. Some data about the consumption of DDT in developing countries are given in table 4. It shows that till a relatively recent date, the use of DDT on a world scale remained particularly high in spite of interdiction in several countries, and it is still widely utilized in tropical countries.

Decisions concerning preventive sanitary measures are usually left to national governments and differ greatly from one country to another. Some countries attempted to replace DDT by Malathion (an OCI) and Propoxat (a CDI). However this operation would be rather expensive and more than one country could not face such experience.

Therefore, in such countries where malaria and trypanosomiasis remain such an acute problem, preventing measures should not involve a total banning.

Two other facets of the toxicology and epidemiology of OCI, are the possibility, on the one hand, to remain for a long time in the environment, eventually contaminating the food chain, and on the other hand to accumulate for a long time in the mammal body fat.

In the USA, DDT occurring in food, mainly of animal origin, can amount

TABLE 4 - Use of DDT in developing countries (year 1970).
(from WHO 1982)

AFRICA			
Country	Quantity (tons)	Country	Quantity (tons)
Egypt	466	Madagascar	152
Ghana	380	Kuwait	176
Upper Volta	20.6	Sudan	16.6
AMERICA		ASIA	
Country	Quantity (tons)	Country	Quantity (tons)
Colombia	347	Cambodia	0.2
El Salvador	6.1	Sri Lanka	270
Guatemala	1.3		
Uruguay	5		

to 0.184 mg per person per day, but the total absorbed dose can be fairly higher in tropical countries (Hayes *et al.*, 1956; Durham *et al.*, 1965). It should be kept in mind that no toxic effect could ever be detected after repeated daily intakes of 1.5 mg per kg body weight, a bit more than 0.1 g per adult, but can reach 35 mg in occupationally exposed workers (WHO, 1982), indicating wide confidence limits. The degradation of DDT into carbon dioxide and hydrochloric acid was more substantially documented (WHO, 1982).

More important toxicological problems arise from the progressive accumulation of OCI in the body fat. It is well known that the accumulation of DDT and its DDE metabolite is much higher in warm countries as exemplified in table 4, in which we compare the results of measurements in Belgium and in some South American, African and Asiatic countries. A large number of parameters should be taken into account and the concentrations (in mg/kg) given in this table are not more than indicative.

Another problem with OCIs is their excretion in mammalian milk after contamination. In Guatemala, this excretion was investigated for a 15-year period in a large spraying area for malaria control. DDT in human mother's milk amounted from 0.3 to 12.3 p.p.m. (Farvar, 1971), which is from 15 to 500 times the acceptable daily intake recommended by WHO (Farvar, 1971). A comparable investigation was made in Iran, where human milk samples from malaria controlled areas were found to contain from 0.4 to 2.5 ppm (8 times higher than the normality) quoted in Farvar and Milton (1973). This raises the problem of toxicity for newborn infants.

Another problem might be of great importance in tropical countries. This is derived from an extensive experimental program on animals. It is known from

experimental data that OCl in particular, and more generally all insecticides, are more harmful to animals suffering from protein deficiencies as is sometimes the case in subtropical and tropical countries as, e.g., Guatemala (Farvar, 1971). This effect has to be extended to domestic mammals, especially cattle.

As concerns long-term effects of OCl, data of the literature, mainly obtained from experiments in mammals are still controversial.

From investigations for mutagenicity some conclusions emerge (review Moutschen *et al.*, 1984). First, the majority of investigated OCl induce chromosome aberrations and mutations in sprayed crops. As for OPI, this is certainly an important inference for agriculture. Even the most toxic compounds, such as Aldrin, Dieldrin and Endrin (table 2) have slight mutagenic effects in all biological systems tested. Chromosome analysis performed on plant worker lymphocytes cultured *in vitro* from Dieldrin did not show any increase as compared with the control population (Dean *et al.*, 1975). In experimental animals, as well as in epidemiological studies of occupational workers, there is certainly limited evidence of carcinogenicity of OCl. In workers exposed for a long time to the most toxic compounds (Aldrin, Dieldrin, Endrin and Telodrin) Jager (1970) did not find any statistically significant incidence difference between occupationally exposed and control groups. With OCl compounds, one factor should be especially taken into account. These compounds have the ability to induce liver mixed functions oxidase, i.e., enzymes of the microsomal fractions. This is the case of DDT (Kolmodin *et al.*, 1969).

In workers exposed to commercial DDT, it was shown that the metabolism of some pharmaceuticals can be activated (Poland *et al.*, 1970; Morgan and Roan, 1974), so that the use of DDT was recommended in some pathological conditions such as hyperbilirubinemia or overdoses of phenobarbital (Rappolt, 1970).

Finally, recent exhaustive reviews concluded that there is no evidence of carcinogenicity of OCl in man. (IARC, 1974; van Raalte, 1977; Sternberg, 1979).

Some embryotoxicity and teratogenicity have been reported in various animals (review in Moutschen *et al.*, 1984). There are no systematic epidemiological studies so far, but only reports of isolated cases. This is certainly a facet of the problem not to be neglected in the countries in which extensive spraying is used.

3. Carbamate Derivative Insecticides (CDI)

A tenth of carbamate derivatives are used as insecticides in tropical countries, but less extensively than the two preceding classes. For this reason, the number of acute poisonings recorded is lower. A great similarity is found between the mode of action of CDI and OPI in animal experiments. In both cases, the toxicity is due to the inhibition of acetylcholinesterase in the central nervous system. However, carbamates do not require metabolic conversion to exhibit toxic action. On the basis of experimental data, several CDI, among which Landrin and Propoxur, were tested in a group of small villages near Kaduna

(Sudan) under the auspices of WHO for spraying and for indoor applications. Slight symptoms were noted in a few workers, but these symptoms disappeared in general after a short time. Some recommendations emerged from this controlled experiment for the safe use of these compounds (WHO, 1979).

If, on one hand, acute poisonings with CDI can be minimized, there is a point worth considering, especially dealing with potential long-term effects. It is a fact that CDI can easily give rise to N-nitroso compounds. This particular reaction has to be taken into account in countries where nitrates are extensively used as fertilizers (see below).

Mainly carbaryl derivatives have been investigated for mutagenicity, carcinogenicity and teratogenicity (review in Moutschen *et al.*, 1984). Some contradictory results were obtained, but potential risks of long-term effects still remain.

B. FUNGICIDES

Fungicides have been recommended in developing countries for several reasons: to increase crop production, to improve crop quality and also for toxicological reasons. In fact, inadequate protection can lead to secondary infestations with noxious weeds or moulds which are able to pollute grains. Some of them are able to exert toxic (including long-term) effects in animals. In particular, mycotoxins (examples of which are given in table 6), which are known to be thermostable (Heinze, 1983) are particularly toxic and highly carcinogenic.

There are certainly good reasons to treat crops with fungicides, but in this class, alkylmercury compounds certainly represent the highest risk in tropical if not in all countries (table 7). Misuse of them has been the origin of disasters.

The tragedy of Minamata in Japan is still in our minds. This was initially due to the pollution of waters with methylmercury, followed by the accumulation of this compound in fishes, where it reached concentrations as high as 20 mg/kg of body weight (Bouquiaux, 1974). It was not surprising that it resulted in a terrible accidental epidemic the far consequences of which are still

TABLE 5 - Classification of some CDI used in tropical countries.

Name	LD50 oral	in rat dermal	WHO classif.	Risks
Carbofuran	8	—	IB	++++
Carbaryl	500	4,000 (rabbit)	IB	++++
Methomyl	17	—	IB	+++
Propoxur	95	2,400	II	++

TABLE 6 - Comparison between acute toxicity and residue tolerances of some important mycotoxins.

Mycotoxin	LD50 oral (mg/Kg)	Species	Residue Tolerance g/Kg
Aflatoxin B1	7.2	rat	5×10^{-5}
T ₂ toxin	3.8	rat	n.d.
Fusarenon X	4.4	rat	n.d.
Malformin	4.0	duck	n.d.
Ochratoxin A	20	rat	n.d.
Patulin	30	mouse	5×10^{-5}
Citrinin	50	rat	n.d.

Modified from Heinze 1983

n.d.: not determined

under investigation. Alkylmercury fungicides are poisons of the nervous system, although in most cases the deleterious effects on kidney are certainly not to be neglected for therapeutic decisions.

The first symptoms observed after acute poisoning are paresthesia of the extremities (hands and feet), ataxia, dysarthria, constriction of the visual field and impaired hearing. There is a long incubation period from the accident to the onset of the first symptoms. It can last for weeks or even months, giving the intoxicated persons a false sense of security. Therefore, the treatment with efficient antidotes is in most cases problematical. In severe poisonings, the above-described symptoms lead to blindness, coma and death. The recovery is rarely complete and such terrible symptoms as ataxia may indefinitely persist. Some of the most well documented epidemiological records after methylmercury poisonings came from Iraq (Bakir *et al.*, 1973). Before 1973, more than 300 cases had been ascribed to methylmercury, and in all tropical areas 1000 to ethylmercury. Cases reported were due mainly to occupational exposures

TABLE 7 - Classification of some fungicides used in tropical countries.

	LD50 oral ppm	in rat dermal	WHO classif.	Risks
Methylmercury acetate	25	—	IA	++++
Phenylmercury acetate	30	—	IA	++++

after seed dressing but also to accidental poisonings when used in fungal skin affections and after suicidal ingestions.

Epidemics of poisonings were also reported in Pakistan, Iraq and Guatemala after ingestion of flour from wheat treated with alkylmercury compounds. The 1972 epidemic in Iraq was particularly catastrophic. Many patients (6530) were hospitalized in rural areas, and 459 deaths were attributed only to methylmercury. The problem was rather complicated by the use of mixtures containing various alkylmercury derivatives. These compounds had to be dosed in the hair of contaminated patients not only for therapeutic decisions, but also for tracing back the times at which the exposure(s) occurred and how severe they were. From these measures in hair and in blood, a good correlation could be made between the dose and the amount of mercury compounds present in bread.

The epidemiological study has some interesting consequences in therapeutic procedures. Classically, 2-3 dimercaptopropanol (British-Anti-Lewisite) is administered after inorganic mercury acute poisonings. However, it was shown before to be ineffective in cases of poisonings with alkylmercury derivatives, because among other things it enhances the concentrations of the compounds in the brain (Dintzis, 1961). As mercury binding agents thiol resin in synergism with N-acetyl-D-penicillamine were shown to be as effective in human beings (Bakir *et al.*, 1973) as compared with animals (Epstein *et al.*, 1963) and it seemed an important step in such poisonings. They should be given as soon as possible after the exposure.

Another hazard in such epidemics arising after massive contaminations of alkylmercury derivatives, either accidental as in the Iraq case or possibly after occupational poisonings after seed dressings, is for infants and also fetus. The problem for fetus is that of a long-term effect (see below), whereas infants can suffer acute poisoning after consuming milk of mothers fed contaminated bread. Yet, newborns from mothers suffering from Minamata disease in Japan were reported to have nervous system damage (Marsh *et al.*, 1977), but the action of mercury derivatives in such cases was through the placental barrier. In the abovementioned Iraq epidemics, no signs of acute poisoning were reported, but the concentration of mercury dose in the infant blood was considered hazardous (Bakir *et al.*, 1973).

Long-term effects of mercury derivatives have been amply worked out (Review Léonard *et al.*, 1984). Mutagenicity has been reviewed by Ramel (1972) and Léonard *et al.* (1981). In all eukaryotic organisms, investigated mercury poisons can produce C-mitosis which result in aneuploidy or polyploidy. In higher plants, Ramel (1972) emphasized the fact that the confidence limit between the highest dose of mercury fungicides at which no effect can be observed and the lowest dose at which they are found is quite narrow. This is an important conclusion for crop production. The reaction of alkylmercury derivatives on plasma membranes (mitochondria, nuclear envelope, Golgi substance, etc.) rich in sulphhydryl groups is well known, and such reactions can lead to the cytological and phenotypical effects mentioned above (Kasuya, 1972-1975). Other observations suggest that these compounds also react directly with chromosomes pro-

ducing clastogenic and mutagenic effects. Comparable results are still contradictory in mammals (reviews in Léonard *et al.*, 1984).

Relevant epidemiological data showing the persistence of clastogenic effects in monitored populations with high occupational risks are not yet available. No carcinogenic effects of alkylmercury fungicides have been demonstrated to date, but observations should be continued. As concerned embryotoxic and teratogenic effects, the situation is not far from dramatic.

From animal experiments, organomercuric compounds are well known for their neurotoxic effects in embryos because the brain of the fetus concentrates mercury. High doses of these fungicides to the fetus can cause brain atrophy or severe mental retardation. This is particularly evident in domestic animals. In man, newborns of mothers suffering from Minamata disease showed typical damage of the central nervous system (Marsh *et al.*, 1977; Harada, 1978). In the Iraq epidemics, this point was not investigated (Bakir *et al.*, 1973).

Hexachlorobenzene (H.C.H.), has been extensively used.

Symptoms of acute poisoning are in general the same as those of OCI (see above). Apart from the general symptoms, there is a special skin sensitivity to UV which results in hyperpigmentation and hypertrichosis. Long-term effects of this drug are important. Some patients lately show neurological symptoms such as paresthesia, motor instability resembling Parkinson's disease or develop leukemia or sarcoma. From 1955 to 1961, this fungicide killed from 400 to 600 persons in Turkey. An epidemiological study of this pathological condition known under the name "porphyria turcica" has been carried out so far.

The origin of epidemics was found to be in contaminated wheat seeds which had been too abundantly sprayed with H.C.H. The extension of the epidemics could not be exactly assessed since only cases admitted in hospitals were recorded and a certain proportion of deaths remained undetected. H.C.H. is persistent in the environment, which leads to bioaccumulation, especially in marine organisms which can concentrate the fungicide up to 10,000 times. More than O.P.I., H.C.H. is known for its high embryotoxicity and its toxicity for infants after contaminating the mother's milk. In the Turkish epidemiological study, 1000 to 2,000 infant deaths were attributed to H.C.H. in mother's milk.

C. HERBICIDES AND DEFOLIANTS

Phenoxyacetic acid derivatives such as 2,4 D. and 2,4,5 T. have a prominent position in tropical countries. The extensive use of such compounds as herbicides and defoliants has almost completely eliminated some dominant plant species of the mangrove forest and also trees of tropical mountain forests.

The toxicity of such defoliant is fortunately low for vertebrates (table 8), but in contrast it is high for other classes of animals, e.g., molluscs. After acute poisonings hexokinase and phosphorylase activity is found to be impaired. This impairment results, among other things, in the deterioration of mitochondria, which in muscles produces microfibrillar lesions leading to a peculiar type of myopathy, i.e., myotonia.

TABLE 8 - Classification of some herbicides used in tropical countries.

	LD50 oral mg/Kg	in rat dermal	WHO classif.	Risks
2,4 D*	610	—	II	++
2,4,5 T	+++	II	—	00C
Paraquat (Gramoxone)	100	80	II	++

* as salt

Acute poisonings can also result in two other syndromes: the neurological syndrome arising from the depletion of the glycogenolysis in the brain and the more complex porphyrine syndrome characterized by the excretion of coproporphyrines.

One of the main problems related to the massive use of phenoxyacetic acid derivatives is the contamination of the commercial formulations by the highly toxic dioxins (tetrachloro 2,3,7,8 dibenzo-p-dioxins).

The countries mostly involved in epidemics are Egypt, Sudan, India, Vietnam and more drastically the Amazonian forest in Brazil (Bouguerra, 1984).

From extensive sprays of the jungle in the years 1981-1982, it became clear that a certain number of deaths, abortions and fetus malformations, such as cranial malformations and spina bifida, could be attributed to sprays containing dioxins as impurities. The Seveso tragedy stimulated new investigations of such classes of compounds, especially of long-term effects. From all the researches, it became obvious that such pesticides are potentially mutagenic, carcinogenic and teratogenic (Review in Wasson *et al.*, 1977-1978).

Acute poisonings after intoxications with another type of herbicide (Paraquat or Gramoxone) occurred in New Guinea in special conditions. Within four years, 18 patients died after drinking contaminated water from containers insufficiently washed. This problem of using old containers is certainly of great importance in tropical countries. Pre-emergence herbicides of the class of triazine raise a special problem of long-term effects. They show low toxicity for mammals but it is demonstrated that in some resistant plant species they can act as pro-mutagens, being slowly metabolized into an ultimate mutagen (Plewa and Gentile, 1982).

Therefore, it is possible that some other herbicides can be further activated by plants into mutagen for animals and man. However, in all these cases impurities present in the commercial formulation should be investigated.

D. HARM OF FERTILIZERS

Criteria of Hygiene of Environment concerning nitrates, nitrites and N-nitroso compounds have been reviewed by W.H.O. (W.H.O., 1980). The world production of nitrogen fertilizers is tremendously high and has still increased during the last decades, e.g., from 15.8×10^6 tons in 1961-1965 to 42.5×10^6 tons in 1974-1975 (report of United Nations 1976). The use of nitrates as fertilizers in high quantities results in an increase of unmetabolized compounds in various plant species — particularly high in such species as lettuce and spinach (Schuphan, 1969). The toxicology of nitrates is well known.

The toxicity is due to the transformation into nitrites, either in the environment or in animal tissue, and the subsequent reaction with hemoglobin leading to methemoglobinemia (review in Hartman, 1982). In the same time, there is a vasodilatation which increases the effects of methemoglobinemia.

Over a concentration of 20‰, it results in a severe hypoxia. Apart from the acute cases, embryotoxicity of nitrates is demonstrated in experiments with laboratory animals: rat (Šbíval and Grüner, 1972) or guinea pig (Sleight and Atallah, 1968). Reproduction is also impaired and high doses (5-10 g/kg) resulted in 100% fetal losses in guinea pig (locyvit.). Therefore, it is admitted that nitrates go through the mother placenta and induce severe methemoglobinemia in the fetus. The first acute intoxication with nitrates was in cattle (Majo, 1895). The economic loss following acute intoxication is especially important in tropical countries (Oehme, 1975). Apart from their use as fertilizers, there are two other possible sources of intoxication with nitrates: as industrial pollutants and as food additives. If the first source is of less relevance in tropical countries (Committee on Nitrate Accumulation, 1972), the second should be carefully taken into account. Nitrates are amply used in food as curing or flavoring agents (review in Ingram, 1974). Low doses produce but slight trouble in adults, the so-called "hot dog disease". It is not the same in infants, in which severe poisonings occur. Apart from the embryotoxicity described above, long-term effects of nitrates are generally related to their potential transformation into nitrites and then into N-nitroso compounds (review in W.H.O., 1980).

Reactions which produce N-nitroso compounds are multiple and complex. In food cured with nitrates these salts can react if reduced into nitrites with amines concurrently produced, among which, methylamine, pyrrolidine and piperidine have been identified. Various reactions lead to various nitrosamines. These latter compounds are abundant in fishes (Sen *et al.*, 1970; Ender and Eeh, 1971) but can also occur in meat.

A second possibility of production of N-nitroso compounds is the nitroso reaction with pharmaceuticals or pesticides, some of which are widely utilized such as triazines (see above) and thiram (Mirvish, 1975). There is a second level of potential action of nitrates reduced in nitrites at low pH. It occurs in the living organisms themselves. For example, it is demonstrated that the concurrent ingestion of nitrates and pyrrolidine (whatever the source of this compound) pro-

duces N-nitropyrrrolidines that result in the formation of the corresponding nitrosamines (Mysliwy *et al.*, 1974). The ultimate production of nitrosamines can be accelerated by a higher speed of production of nitrites. This is the case when bacteria of the digestive tract particularly rich in nitroreductase accelerate the process. The rumen of bovine stomach has a high content in such bacteria (Oehme, 1975), and in man such bacteria proliferate in intestines (Hawksworth and Hill, 1971), from which nitrosamines can diffuse to other organs reacting as a target. The acute toxicity of N-nitroso compounds is of less importance compared with long-term effects. The carcinogenicity and mutagenicity of nitrosamines have been unquestionably demonstrated in animal experiments (W.H.O., 1980). A number of epidemiological studies have been performed. Some data are summarized in table 9. The first aim is to correlate the frequency of some types of tumors with the content in nitrosamines, e.g., in food. For naso-pharynx and esophagus tumors, no correlation could already be definitely established. For stomach, the results are somewhat ill defined. In the first set of researches (a) no correlation was obtained but the hypothesis was put forward of a direct local action of nitrosamides on gastric mucosae. Nitrosamides would be formed in the stomach (of acidic pH) with amides arising from food.

In the second set of researches (b), an attempt was made to correlate the frequency of stomach cancers with the nitrate contents of soil and water in Colombia, Chile and the United Kingdom, but in these studies no correlation could be obtained. In fact, in epidemiological studies the number of variables is generally so great that we cannot safely base the long-term effects of N-nitroso compounds on the results obtained with laboratory animals (see above). Moreover, there are reasons to believe that the problems of long-term effects are more drastic in tropical countries.

TABLE 9 - Epidemiological reports on several cancers and the possible role of nitrosamines in some tropical countries.

Type of cancer	Country	References
Naso-pharynx	{ Southeast Asia	Clifford 1970, Fong and Chang 1973
Esophagus	{ South Africa Iran China	Berrel <i>et al.</i> , 1966
Stomach	Colombia	{ Correa <i>et al.</i> , 1975 4) Haenszel and Correa 1975
Stomach	{ Colombia Chile	{ Hawksworth <i>et al.</i> , 1974 b) Hill <i>et al.</i> , 1973 Zaklvar and Wetterstrand 1975

EPILOGUE

After reviewing some toxicological and epidemiological problems raised by the use of pesticides in tropical countries, some general ideas emerge.

The toxicological studies reviewed in the present context aim to show the risks of acute poisonings for each class of pesticides and therefore what could be avoided, or handled with care or possibly replaced if not excessively expensive.

Toxicological and epidemiological studies in tropical countries revealed that the highest risk is incontestably acute poisonings, the main reasons for that situation being free sale of pesticides, abusive use and not sufficient knowledge of the parameters involved, and also too numerous suicides. It should be underlined that in tropical countries there is a policy of subvention for sale of pesticides aiming to promote agriculture, which eventually leads to exaggerated and uncontrolled utilization.

The acute poisoning of animal population is also, more than in industrialised areas, to be taken into account. We are dealing here with animals used as food, not only bovines but also wild animals such as fishes.

Besides immediate effects, long-term effects, although deserving consideration as evidenced in the previous surveys (*loc. cit.*), are not at present an emergency in tropical countries. In fact, the evidence of carcinogenicity, mutagenicity and teratogenicity of some of the pesticides arises from laboratory animal experiments. The more complex epidemiological data are generally difficult to interpret.

A quite general idea, which emerges as well from agricultural studies as shown in several sections of the present symposium as from toxicological or medical investigations, is, as stated by Smith (see Davies *et al.*, 1978), the need for what he named with the neologism: « Agromedicine ». The definition is as follows. It is "the integrated interdisciplinary application of the skill and knowledge of agriculture, applied chemistry and medicine to the production of an adequate and wholesome food supply for the welfare of man".

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