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**Past and Present of Chagas Vector
Control and Future Needs**

Position Paper

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Communicable Diseases
WHO Pesticide Evaluation Scheme (WHOPES)**

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1. Introduction

Chagas disease or American trypanosomiasis occurs on the American continent in the area between 42° N and 45° S latitudes, where it infects 16-18 million people. Some 100 million people, a quarter of all the inhabitants of Latin America, are at risk of contracting the disease (1).

Chagas disease is a chronic and incurable parasitic infection that causes disability and death. It is caused by a flagellate protozoan, *Trypanosoma cruzi*, which is transmitted to humans in the feces of blood sucking triatomine bugs. There are 3 genera of triatomines incriminated in the transmission of Chagas disease: *Triatoma*, especially *T. infestans*, *T. dimidiata* and *T. sordida*; *Rhodnius*, especially *R. prolixus* and *R. pallescens* and *Pastrongylus*, especially *P. megistus* (2).

The number of disability-adjusted life years lost (DALYs) because of Chagas disease amounts to 2,740,000 and represents the third largest tropical disease burden after malaria and schistosomiasis in Latin America (3). No treatment is available for the chronic forms of the disease and there is no acquired immunity. Chemical control of the vectors appears to be the best way to reduce the incidence of the disease (2, 3). Chemical control has been based principally on spraying dwellings and peridomiciliary areas with insecticide formulations applied by professional sprayers. The active ingredients used since the 1960's were chlorinated hydrocarbons, organophosphorus, carbamate and pyrethroid insecticides. Chemical vector control programmes at the national level have been implemented in Argentina, Brazil and Venezuela.

Activities for the control of Chagas disease vectors involve three stages (5):

1. *Preparatory phase*: Includes the mapping of the area to be treated, the programme of control activities and estimation of resources.
2. *Attack phase*: In this phase a blanket insecticide spray coverage of infested houses takes place, followed by a second spraying of re-infested houses no more than 6 months later.
3. *Surveillance phase*: When the objective of the attack phase, i.e., interruption of transmission, has been reached vigilance activities are performed to detect and control residual foci of triatomines.

Control activities based on the above 3 stages are not always strictly followed. In some cases the second spraying of the attack phase is not carried out or a mix of attack and surveillance phases are performed.

2. Historical background

The wartime success of DDT in controlling malaria (6) stimulated Latin American entomologists to test this insecticide in the 1950s for the control of Chagas vectors. Unexpectedly, DDT had to be discarded because of its low level of efficacy against triatomine vectors of Chagas disease. The low triatomocidal power of DDT was due to two degradation pathways in *T. infestans* (7, 8). These pathways are mediated by a DDT – dehydrochlorinase and by a DDT hydroxylase which metabolize DDT to DDE and kelthane respectively (7,8). Delayed penetration of DDT in starved nymphs of *T. infestans* was shown to be a

complementary cause of the tolerance to this insecticide (9).

After the unexpected failure of DDT, the first option among the chlorinated hydrocarbons was HCH, which was successfully introduced for the control of the Chagas disease vectors in 1947 (10).

3. Insecticides used

3.1 Chlorinated hydrocarbons

DDT was first introduced for triatomine control and rapidly replaced by HCH. This product is a mixture of five isomers of hexachlorocyclohexane (11). The γ isomer, lindane is the active component of HCH. This was the only isomer with insecticidal activity against *T. infestans* (B. D'Agostino and E. Zerba, unpublished data).

The dosage of lindane needed for the control of Chagas disease vectors was 500 mg/m². The treatments were expensive and time consuming because two successive sprays cycles per year was necessary for a successful control. The initial application eliminated the nymphs and adults while the second, 1 to 6 months later, eliminated the nymphs born from eggs hatched before the end of the residual activity of the insecticide.

Venezuela introduced dieldrin in 1947 for the control *Rhodnius prolixus*, the principal vector in the region (10). The use of dieldrin was a consequence of the DDT failure in the initial control actions in Venezuela to reduce the incidence of Chagas disease.

In the early 1960's the enormous impact of Rachel Carson's book "Silent Spring" drew attention to the

potential of chlorinated hydrocarbon insecticides to adversely affect the environment. The high chemical stability and the potential toxicological and ecotoxicological risk of chlorinated insecticides caused their progressive substitution by compounds with more favorable properties. Organophosphorus and carbamate insecticides were less persistent, non-bioaccumulative alternative insecticides for the control of Chagas disease vectors.

3.2 Anti-cholinesterase compounds

Organophosphorus and carbamate insecticides kill insects by inhibiting acetylcholinesterase, with consequent disruption of nervous activity caused by accumulation of acetylcholine at post-synaptic nerve junctions (11). Propoxur was the first anti-cholinesterase insecticide used for the control of triatomine vectors of Chagas disease. The triatomocidal effect of this carbamate was established in 1968 and the initial field trials were performed in Chile between 1969-1971 (9).

The phosphorothionates malathion and fenitrothion were introduced in 1975 into Chagas vector control programmes. These anti-cholinesterase compounds with ovicidal action (12) had lower vapour pressure and a higher initial impact of control than HCH, allowing spacing between applications of 1 year. Many phosphorothionates have the disadvantage of a strong and unpleasant smell, which results in villagers' resistance to the house treatments. These compounds are a good alternative for treatments in outhouses and other peridomestic structures (13).

The organophosphate DDVP had a limited use as a "dry fog" or as slow release formulations. Other anti-

cholinesterase compounds, such as pyrimiphos methyl and bendiocarb were evaluated at the laboratory level, but not used in regular campaigns against the vectors of Chagas disease.

In Table 1 the LD₅₀ values of anti-cholinesterase compounds obtained in fifth-instar nymphs of *T. infestans* are shown (14,15).

Table 1 – Triatomicidal effect of anti-cholinesterasic insecticides on fifth-instar nymphs of *T. infestans* by topical application.

Insecticide	LD ₅₀ (µg/g body weight)	Confidence Limits
Malathion	49.2	37.6 – 64.4
Fenitrothion	5.6	2.5 – 12.5
Pirimiphos methyl	12.8	7.5 – 21.9
Dichlorvos	39.5	37.0 – 42.0
Propoxur	18.5	15.1 – 24.6
Bendiocarb	20.0	15.3 – 26.2

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3.3 Pyrethroids

Synthetic pyrethroids are neurotoxins acting on the axons in the peripheral and central nervous systems by interacting with sodium channels in mammals and/or insects. Because of their great insecticidal activity, their low application rates and their rapid degradation in the environment, these compounds have been successfully used for the control of household pests and insects of public health importance (16). Allethrin was the first

commercially successful pyrethroid, introduced in 1949. Allethrin and other photolabile compounds principally obtained by esterification of chrysanthemic acid constitute the first generation of pyrethroid compounds.

These first generation pyrethroids were not successfully used in the field for the control of Chagas vectors despite excellent triatomocidal activity in laboratory bioassays, as shown in Table 2 (17). The failure of first generation pyrethroids for Chagas vector control was principally caused by their lack of residual activity.

Table 2 – Triatomocidal effect of some pyrethroid insecticides by topical application to fifth-instar nymphs of *T. infestans*.

Insecticide	LD ₅₀ (µg/g body weight)	Confidence Limits
Bioresmethrin	0.6	0.3 – 1.4
N – Phemothrin	2.8	2.2 – 3.7
Cyphenothrin	2.9	2.8 – 3.0
Bioallethrin	10.7	7.1 – 16.2
Allethrin	90.7	77.4 – 106.4

References 16 and 17

Deltamethrin first described in 1974, was the first photostable pyrethroid tested on triatomines in the laboratory. It was highly toxic to *T. infestans* (18). Deltamethrin and cypermethrin have been successfully applied in the field for Chagas vector control in Argentina and Brazil since 1980 (10). Permethrin had a limited use in Brazil because the dosage needed for adequate control resulted in expensive treatments, but its, *cis* isomer was

recently described as one of the most toxic pyrethroids to *T. infestans* (19,20). The difference in toxicity to *T. infestans* between *cis-trans* permethrin and the isolated *cis* isomer shown in Table 3 was explained by antagonism between the isomers (20), i.e., the less active *trans* isomer produces an antagonistic effect which masks the high toxicity of the *cis* isomer when they are simultaneously applied to nymphs of *T. infestans*. These results open up the interesting possibilities for the *cis* isomer of permethrin as a new tool for control of the vector of Chagas disease. The selectivity of *cis* permethrin is better than that of deltamethrin.

In the 1990's pyrethroids used in Chagas vector control were restricted to cypermethrin and a select group of third generation cyanopyrethroids with high triatomocidal activity (Table 4).

Table 3 – Toxicity of *cis:trans* permethrin topically applied to nymphs of *T. infestans*.

Cis : trans	LD ₅₀ (ng/insect)	
	Third-instar nymphs	Fifth-instar Nymphs
100 : 0	5.8	16.8
82 : 18	11.2	47.5
24 : 76	139.6	325.3
0 : 100	144.0	899.8

Adapted from reference 20

Table 4 – Triatomicidal effect of the principal pyrethroid insecticides used at the present time in Chagas vector control topically applied to fifth-instar nymphs of *Triatoma infestans*.

Insecticide	LD ₅₀ (µg/g body weight)	Confidence Limits
Deltamethrin	1.54	0,85 – 2,48
Beta-cypermethrin	1.56	0,93 – 4,34
Beta-cyfluthrin	0.32	0,18 – 0,46
Lambda-cyhalothrin	0.11	0,06 – 0,21
Cypermethrin	2.86	0,95 – 6,67

Second generation pyrethroids are the group of isomeric mixtures of photostable compounds such as cypermethrin and permethrin. Pyrethroids belonging to the third generation are the more active isomers obtained by isomeric enrichment.

The third generation pyrethroids currently used for Chagas vector control include deltamethrin, lambda-cyhalothrin and beta-cyfluthrin. The successful results of recent laboratory bioassays, field trials and national campaigns of Chagas vector control in Argentina recently allowed the incorporation of beta-cypermethrin to this pyrethroid group (21).

3.4 Other insecticides

Many compounds with a wide variety of chemistry possess juvenile hormone (JH) activity for different insect orders. The activity of these JH compounds is specific to each order or even family of insects (22). In the case of *T. infestans* the fifth-instar nymphs are the most susceptible

to JH analogues (23). In spite of the high selectivity and effectivity against triatomines established in JH experimental compounds (24, 25) and commercial products such as fenoxycarb (23) these particular type of insect growth regulators (IGR) are not used in the field at the present time for the control of Chagas disease vectors. The principal criticism to the use of JH insecticides in Chagas vectors control is their mode of action. The interference with normal metamorphosis performed by JH compounds could produce abnormalities after moult and delayed ecdysis (23). These effects result in delayed population control instead of fast mortality.

In summary, JH compounds would tend to prolong the disease-transmitting nymphal stage and, hence, show little promise for the control of Chagas disease vectors. But their complementary use with neurotoxic insecticides with established toxicity to triatomines should be explored. Since the fifth-instar nymph is the stage least susceptible to neurotoxic insecticides and since abnormal moulted individuals caused by JH compounds could present a low vector potential, mixed formulations of the two types of insecticides may well result in a satisfactory integration of these tools.

Anti-feeding compounds are substances which are not necessarily food repellents but cancel out the signal to the appropriate organ in the insect to initiate feeding on the host. After contact with an anti-feedant the insect may starve to death. It was demonstrated that N-ethylmaleimide (NEM) and other sulfhydryl reagents inhibited the feeding response of *T. infestans* (26). *Triatoma* feeding was also deterred when a gauze cloth impregnated with NEM was located between the food source and the nymphs. The anti-feedant effect is attributed to a receptor blockage produced by sulfhydryl reagents (26). A series of *cis* isomers of methyl esters of

N-substituted maleamic acid were synthesized and their anti-feeding activity by topical application on 5th instar nymphs of *T. infestans* was demonstrated (27). Likewise, the continuous exposure of *T. infestans* experimental populations to anti-feeding maleamates produced a significant reduction in the insect and egg numbers (28).

Population management by anti-feedants could be considered as an alternative method of Chagas disease vectors control. As in the case of JH insecticides, anti-feedant compounds, deserve more research as a complementary tool for integrated programmes of triatomine control.

4. Insecticide formulations

After being manufactured in their technical grade commercial form, insecticides have to be formulated. That is, they are processed into a usable form for direct application or for dilution followed by application. The formulation process of an insecticide improves its properties of storage, handling, application, effectiveness or safety. The term formulation is usually reserved for commercial preparation prior to actual use and does not include the final dilution in the application equipment. The principal ingredients of an insecticide formulation include the biologically active principle, clays, solvent diluents, surfactants and polymers. The factors, which influence the choice of formulations, are the physical and chemical properties of the insecticide, type of application and economics (29).

Until the late 1980s the most common formulations for Chagas disease campaigns were wettable powders (WP) and emulsifiable concentrates (EC).

WPs are constituted by mixing insecticides with carriers such as talc or clay and contain a wetting agent. ECs, however, are generally constituted by dissolving insecticide in an oil or aromatic solvent and contain enough emulsifier to mix readily with water. The viscosity of the oily carrier influences the toxicity of the insecticide in *T. infestans*. The lighter the carrier oils, with lower values of viscosity, the faster the insecticide penetrates through the insect tegument achieving an enhanced toxic effect (30). ECs of organophosphorus compounds like malathion and fenitrothion, the carbamate propoxur and the pyrethroids deltamethrin and cypermethrin have been used in national campaigns performed in Argentina and Brazil for triatomine control (31).

Flowable or suspension concentrate (SC) is a dispersion of finely ground solid insecticide in water. The formulation of aqueous concentrated suspensions of solid insecticides requires the use of powerful dispersing agents, which keep the particles in a deflocculated state. Flowable formulations have been used recently for the control of Chagas. Because of their toxicological and practical advantages this type of formulation is now considered the best option in national campaigns of Chagas vector control. On the other hand in the diluted suspension the insecticide is associated with solid granules that are not absorbed by porous surfaces extending its residual activity (32).

Other types of formulations designed to be applied by professional sprayers, such as ultra low volume (ULV) formulations or dry dusts, are not currently used in Chagas vector control (31).

The formulations and the dosages used in field applications of the most used third generation pyrethroids

at the present time in governmental campaigns of Chagas disease vectors are shown in Table 5.

Table 5 – The common used third generation pyrethroids for indoor residual spraying against Chagas vectors.

Pyrethroid	Formulation	Field Concentration (mg/m²)
Deltamethrin	Suspension concentrate	25
Lambda-cyhalothrin	Wettable powder	35
Beta-cyfluthrin	Suspension concentrate	25
Beta-cypermethrin	Suspension concentrate	50

5. Innovative tools

In recent years with the support of the Tropical Disease Research Programme (TDR) of WHO, two new vector control tools have been developed for use against Chagas disease: a fumigant canister and paints that incorporate insecticides in a slow release formulation.

The Fumigant canister was developed in Argentina in the Research Center of Pest and Insecticides (CIPEIN) (1, 5, 13, 16, 33). Different formulations of this device contained different type of insecticides. The latest version of the fumigant canister (CIPEIN – PF-6) was introduced to the market in 1994. Its principal active is beta-cypermethrin. The fumigant mixture includes beta-

cypermethrin incorporated into the mixture using adequate protective measures to avoid thermal or chemical decomposition during the combustion (34).

Although fumigant canisters were initially designed to be used during the surveillance phase their success in the centralized or community based attack phase has been demonstrated in different field trials (34). However, the principal roll of the fumigant canister could be to make the surveillance phase of Chagas vector programs more sustainable in areas where domiciliary vectors are the major targets, thereby improving the overall efficiency of the programs (35). The use of fumigant canisters is expected to reduce the financial costs of vector programs and to create opportunities for wider participation of the community at risk in Chagas disease control activities (34, 35).

At present, the fumigant canister for Chagas disease vector control is used in governmental campaigns only in Argentina. In 1991 the Ministry of Health of Argentina adopted the CIPEIN – PF-5 version of the fumigant canister in its national Chagas disease strategy and during the period of 1991-1995 the government of Argentina purchased a total of 495.000 canisters (35). According to the analysis of Fujisaki and Reich (35), the extensive use of the fumigant canister by the Argentinean Ministry of Health since 1991 probably contributed to the reduction of the prevalence of Chagas disease in recent years in Argentina.

Slow release formulations of insecticidal paints, mostly based on organic polymers, have been developed and tested in the control of Chagas Vectors in Brazil with the support of TDR (1, 13, 31). In field trials of a malathion/polyvinyl acetate slow – release emulsion paint had long indoor efficacy. The stability and adherence to

the substrates of the paints could be an advantage over conventional formulations, preserving insecticide effect where other formulations would probably be washed off or sink into the underlying substrate (31). This property could make the paints an effective alternative for the control of Chagas vectors located in peridomestic areas.

6. Insecticide resistance

Despite prolonged and intensive control campaigns against Chagas vectors few studies have been made on the possible development of insecticide resistance in triatomines (36).

In Argentina a strain of *T. infestans* resistant to malathion was selected and esterases were involved in the resistance (37). Resistance to dieldrin in *R. prolixus* from Venezuela, reported in 1971, is the first well-documented evidence of field resistance. Dieldrin resistance was first detected in the state of Trujillo and later in the states of Yaracuy, Tachira, Cojedes y Portuguesa (38, 39).

High resistance ratios to gamma HCH (>1200) and dieldrin (550) occurred in a strain of *R. prolixus* (Santo Domingo) as measured by topical application of the insecticides. This strain was susceptible to pyrethroids (40).

A Venezuelan *R. prolixus* strain from Carabobo had high resistance to five pyrethroids: resistance ratios ranged between 12.4 for cypermethrin to 4.5 for lambda-cyhalothrin (41). This was surprising, as *R. prolixus* control was mostly done with organochlorines in Venezuela (38). In the State of Carabobo house spraying employed

dieldrin, HCH and fenitrothion. Exposure of *R. prolixus* to pyrethroids might be due to their intensive use for mosquito control in Carabobo State (Molina de Fernández D. personal communication). Deltamethrin resistance in this *R. prolixus* strain was strongly reduced by piperonyl butoxide (PBO) pretreatment suggesting involvement of mixed function oxidases in pyrethroids resistance (41).

A *T. infestans* strain from Porto Alegre, Brazil, showed higher resistance to deltamethrin (7x) than to cypermethrin (3.3x) or beta-cyfluthrin (3.6x) but was normally susceptible to beta-cypermethrin and lambda-cyhalothrin (40). Pyrethroid resistance in this strain was associated with intensive use of deltamethrin and cypermethrin for control of Chagas disease in Brazil since 1982 (42). PBO synergism of deltamethrin resistance in this strain, suggests oxidative metabolism as a cause of resistance (40).

A program of detection of resistance to deltamethrin in Argentina is now in progress. After a screening performed by topical application of deltamethrin according to the WHO protocol (43), four resistant strains were found in San Luis, Mendoza, La Rioja and Catamarca (Picollo M.I. and Zerba E., unpublished results). The resistance monitoring in Argentina is performed as part of a more extensive Latin American program sponsored by the TDR of WHO.

7. Future trends

Important progress in the control of Chagas disease in South America started in 1991 when the Southern Cone Initiative was launched by Ministries of Health of Argentina, Brazil, Bolivia, Chile, Paraguay and Uruguay. This Initiative is coordinated by the Pan American Health

Organization, Regional Office for the Americas of the WHO (1, 44, 45). In 1997 governments outside the Southern Cone launched the Andean and Central American Countries Initiatives. These initiatives represent a big effort by Latin American countries to interrupt transmission of Chagas disease by eliminating its vector (3, 44,45).

The impact of these measures is becoming apparent, with a reduction in morbidity and mortality, especially in Argentina, Brazil, Chile and Uruguay (3, 44, 45). Future control actions should be adapted to new situations. Entomological research should be focused on different aspects related to monitoring of low density triatomine populations and on non-domiciliated species such as studies on house colonization, population dynamics and genetical or behavioural research aimed at their control.

For efficient vector control it is necessary to complete the studies of insecticide efficacy especially in the Andean and Central American countries; to do research on the chemical communication of triatomines; to develop baits and other tools useful in the control of low density populations; and to intensify the programmes of resistance monitoring in all the Latin American countries.

The control tools for interrupting the domestic cycle of Chagas disease are available. Sustained implementation of vector control measures is expected to achieve the interruption of vector transmission of Chagas disease in the near future. Field and laboratory research, especially performed in Latin American countries, should be a support of this objective.

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