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**TDR's Contribution to
the Development of
the Fumigant Canister
for Controlling
Chagas Disease**

**Third
External
Review**

*UNDP/World Bank/WHO
Special Programme for Research & Training
in Tropical Diseases*



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**TDR's Contribution to the Development
of the Fumigant Canister for Controlling
Chagas Disease**

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TDR's contribution to the development of the fumigant canister for controlling chagas disease

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Purpose of report

This report reviews how the fumigant canister, a new tool to prevent the spread of Chagas disease, was developed in Argentina with the support of the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR). The objective of this report is to identify:

- The contributions made by TDR at different stages of the development of the fumigant canister;
- Major factors that fostered or hindered TDR's contributions; and
- Implications of these findings for TDR's mandate to develop new tools for control of tropical diseases.

Following an introduction to Chagas disease, the report is divided into three parts. First, it describes the problems identified by TDR in the control of Chagas disease. Second, it describes the activities undertaken by the main actors at seven stages of development of the fumigant canister. And finally, it draws some conclusions and lessons for TDR in future.

Information for the report was collected through a review of documents and the published literature, as well as interviews and correspondence with key persons who were involved in the development process.

Introduction to Chagas disease

Chagas disease, also known as American trypanosomiasis, occurs only in the Americas and has been registered from the southern United States to the Province of Chabut in Argentina.¹ The disease is caused by a flagellate protozoan parasite, *Trypanosoma cruzi*, which is transmitted to humans through bloodsucking triatomine reduviid bugs. WHO estimated in 1991 that 16 million to 18 million people were infected with *T. cruzi* in the Americas, and an additional 90 million people (i.e. one-quarter of all the population of Latin America) were at risk of infection.² It is estimated that Chagas disease causes more than 45,000 deaths per year in the region.³

¹ Prata, A. Chagas' Disease. *Disease of Latin America*. 8 (1):61-76, 1994.

² WHO Expert Committee. *Control of Chagas Disease*. WHO Technical Report Series 311, 1991.

³ TDR. *Tropical Disease Research 1991-92, Eleventh Programme Report*, p. 67.

Clinical symptoms of Chagas disease can be divided into three stages. The acute stage involves nonspecific reactions, or can be asymptomatic, resulting in difficulties in early diagnosis of the disease.⁴ During the second, latent, stage, which can last for an indefinite period of time, most infected persons do not experience clinical symptoms, and electrocardiograms and chest X-rays cannot detect the disease. However, serological tests for Chagas disease remain positive, and thus patients become an important reservoir of the infection for maintaining the life cycle of the parasite. After this silent period, about 30 per cent of infected persons progress to the chronic stage, which takes three forms and causes irreversible damage to the cardiac, digestive or neurological tissues.⁵

People in rural areas are routinely exposed to the insect vectors of the disease in their everyday environment, putting them at a particularly high risk of infection.⁶ Chagas disease is most common in poor communities where houses built of basic materials, such as a roof made from dried straw and mud-plastered walls, provide ideal spots for harboring domiciliary triatomine reduviid bugs. In recent years, Chagas disease has also become a growing concern in urban areas as more and more people migrate from the rural areas to the cities and the infectious agent enters the blood supply.

The impact of Chagas disease on individuals, families and society is high, because it often incapacitates people at the peak of their economically productive years. According to an estimate by the World Bank, the burden of Chagas disease in Latin America ranked fourth among all the region's infectious diseases, measured in terms of lost years of healthy life (2,740,000 disability adjusted life years). Only acute respiratory infections, diarrhoeal diseases and AIDS claimed greater burdens.⁷

Two drugs, nifurtimox and benznidazol, can be used for treatment at the acute stage, but difficulties in early diagnosis and the possibility of adverse effects make these drugs unsuitable for mass treatment of Chagas disease. There is no vaccine available for the disease.⁸ Thus, vector control is one of the few viable means of interrupting transmission of the parasite, besides housing modifications and community health education.⁹

⁴ WHO Expert Committee. *Control of Chagas Disease*. WHO Technical Report Series 311, 1991.

⁵ Moncayo, A. Chagas Disease: Epidemiology and Prospects for Interruption of Transmission in the Americas. *World Health Statistics Quarterly*. 45:276-279, 1994.

⁶ Dias, JC. Chagas Disease Control in Brazil: Which Strategy after the Attack Phase? *Annales de la Société Belge de Médecine Tropicale*. 71(Suppl 1):75-86, 1991.

⁷ The World Bank. *World Development Report 1993: Investing in Health*. New York: Oxford University Press, 1993.

⁸ Because *T. cruzi* antigens can stimulate autoimmunity, the development of a safe and effective vaccine is expected to be extremely difficult.

⁹ Schofield, CJ. Control of Chagas' Disease Vectors. *British Medical Bulletin*. 41(2):187-94, 1985.

1. Problems and priorities

The disease, the causative agent (*T. cruzi*), and the insect vectors of Chagas disease were all discovered by Carlos Chagas, a Brazilian parasitologist, in the early 20th century.¹⁰ However, in 1977 when the TDR Scientific Working Group (SWG) on Chagas Disease began its activities, there were still a number of problems in the control and treatment of Chagas disease. TDR's report for 1985-86 reviewed the problems that TDR faced in the mid-1970s for this disease:

Epidemiology and natural history of disease were not fully understood. Diagnostic methods were not simple, sensitive or specific enough, nor were they standardized. Methods of characterizing different *T. cruzi* strains were lacking and there were no *T. cruzi* reference strains. The drugs available for therapy were inadequate and few systematic attempts were being made to develop better drugs. The pathology of the disease was poorly understood, progress being hampered, among other things, by the absence of suitable animal models. Blood transfusion was recognized as a serious transmission factor, but tests for detecting infected blood were not satisfactory, nor was the compound used for treating transfusion blood, gentian violet, entirely acceptable. Finally, vector control was based almost exclusively on the use of chemical insecticides.¹¹

From this long list of problems, the Scientific Working Group on Chagas Disease in 1977 identified the main objectives for TDR's activities on Chagas disease, and established three sub-committees that were responsible for selected areas as follows:¹²

- Parasitology, Biochemistry and Drug Development (CHEMCHA):
 - development of new drugs;
 - improvement of the use of existing drugs.

- Immunology and Immunopathology (IMMCHA):
 - improvement of methods to eliminate the parasite from blood banks;
 - discovery of inhibitors of immunopathology.

¹⁰ Busvine, JR. The Impacts of The New Insecticides, part 3 of *Disease Transmission by Insects: Its Discovery and 90 Years of Effort to Prevent It*. Springer-Verlag. 1993.

¹¹ TDR. *Tropical Disease Research, Eighth Programme Report 1985-86*. pp. 90-91.

¹² In 1989, three Steering Committees were merged into a single Steering Committee on Chagas Disease.

- Epidemiology, Vector Biology and Control (EPICHA):
 - improvement of diagnostic tests;
 - improvement of vector control methods and insecticides; and
 - better understanding of the geographical distribution, prevalence and clinical varieties of Chagas disease and of the distribution of its vectors.¹³

At the same time, TDR recognized that an advanced level of research capacity on Chagas disease already existed in Latin America. Therefore, TDR defined its role mainly as one of coordinating major activities and standardizing research procedures.¹⁴ Thus, the first priority was to promote the standardization of epidemiological, clinical and diagnostic procedures and parameters so as to establish a scientific basis for collecting comprehensive data about the disease. The development of a suitable animal model and the definition of technical guidelines for immunoprophylactic and chemotherapeutic trials were also recognized as important priorities.¹⁵

Of the three sub-committees within the Scientific Working Group on Chagas Disease, it was EPICHA which oversaw the development process of the fumigant canister¹⁶, and therefore the remainder of this section focuses on its activities. EPICHA identified the following five priority areas for research:

- geographic distribution and prevalence of the disease;
- factors influencing prevalence of the disease and the dynamics of its transmission;
- evolution of infection and mechanism responsible for chronic lesions and their clinical forms;
- standardization of the criteria for diagnostic tests of higher sensitivity and specificity; design and evaluation of procedures for epidemiological surveillance assisted by community participation; and
- reduction of the contact between humans and vectors by, for example, the development of materials for improving housing and a search for better insecticides.

In its program report for 1981-82, TDR stated that "the only practical measures of controlling Chagas disease were those aimed at interrupting the domestic and peridomestic vector-host cycles by attacking the insect with the use of insecticides."¹⁷ Although housing modifications were known to be an effective long-term solution for interrupting the domestic cycle of transmission, they were also expensive and not feasible for immediate large-scale use.¹⁸ There are significant differences among the

¹³ TDR. *Fourth Annual Report (1 June 1979-30 June 1980)*, pp. 144-54.

¹⁴ TDR. *Third Annual Report (1 July 1978-30 June 1979)*, p. 95.

¹⁵ TDR. *Fourth Annual Report (1 July 1979-30 June 1980)*, p. 143.

¹⁶ From this reason, the remaining part of this report focuses on EPICHA, leaving those activities under CHEMCHA and IMMCHA prior to 1989. Since the reorganization in 1989, the Steering Committee on Chagas Disease reviews all TDR's activities for the disease.

¹⁷ In-Depth Report of the SWG on Chagas' Disease to STAC, 1979-81. *TDR Progress Report 1981-82*, p. 142.

¹⁸ Prata, A. Outlook for Chagas' Disease: Insecticides for Short-Term, Improved Housing for Long-Term. *Indian Journal of Pediatrics*. 39:123-125, 1972.

vectors of Chagas disease depending on the endemic area, and these differences directly affect the feasibility of vector control: *T. dimidiata*, *T. sordida*, *T. brasiliensis*, and *Panstrongylus megistus* are both domestic and sylvatic, which pose difficulties for controlling these vectors with insecticides. On the other hand, *T. infestans* and *Rhodnius prolixus* are almost exclusively domiciliary, and therefore excellent targets for vector control programs. The long life cycle and the slow rate of reproduction of triatomine reduviid bugs also present a favorable condition for the intensive use of insecticides, because these characteristics make it unlikely that the vectors will develop resistance to insecticides.

Typically, vector control activities for Chagas disease involve three stages:

- *preparatory phase* for mapping and programming of activities and estimation of resources;
- *attack phase* during which a massive first insecticide spraying of houses takes place, followed by a second spraying 3 to 6 months later and further evaluations for selective re-spraying of reinfested houses; and
- *surveillance (or vigilance) phase* for the detection of residual foci of triatomines after the objective of the attack phase has been reached.¹⁹

Although the usefulness of insecticides vector control in Chagas disease had been known since the mid-1940s,²⁰ Chagas disease control programs prior to the early 1980s were constrained by a number of operational and financial difficulties. Successful control programs required a sustained level of financial and political commitment throughout the three phases, and campaigns were often interrupted by a lack of resources and administrative constraints, allowing treated areas to become reinfested and so enabling the spread of new infection.²¹

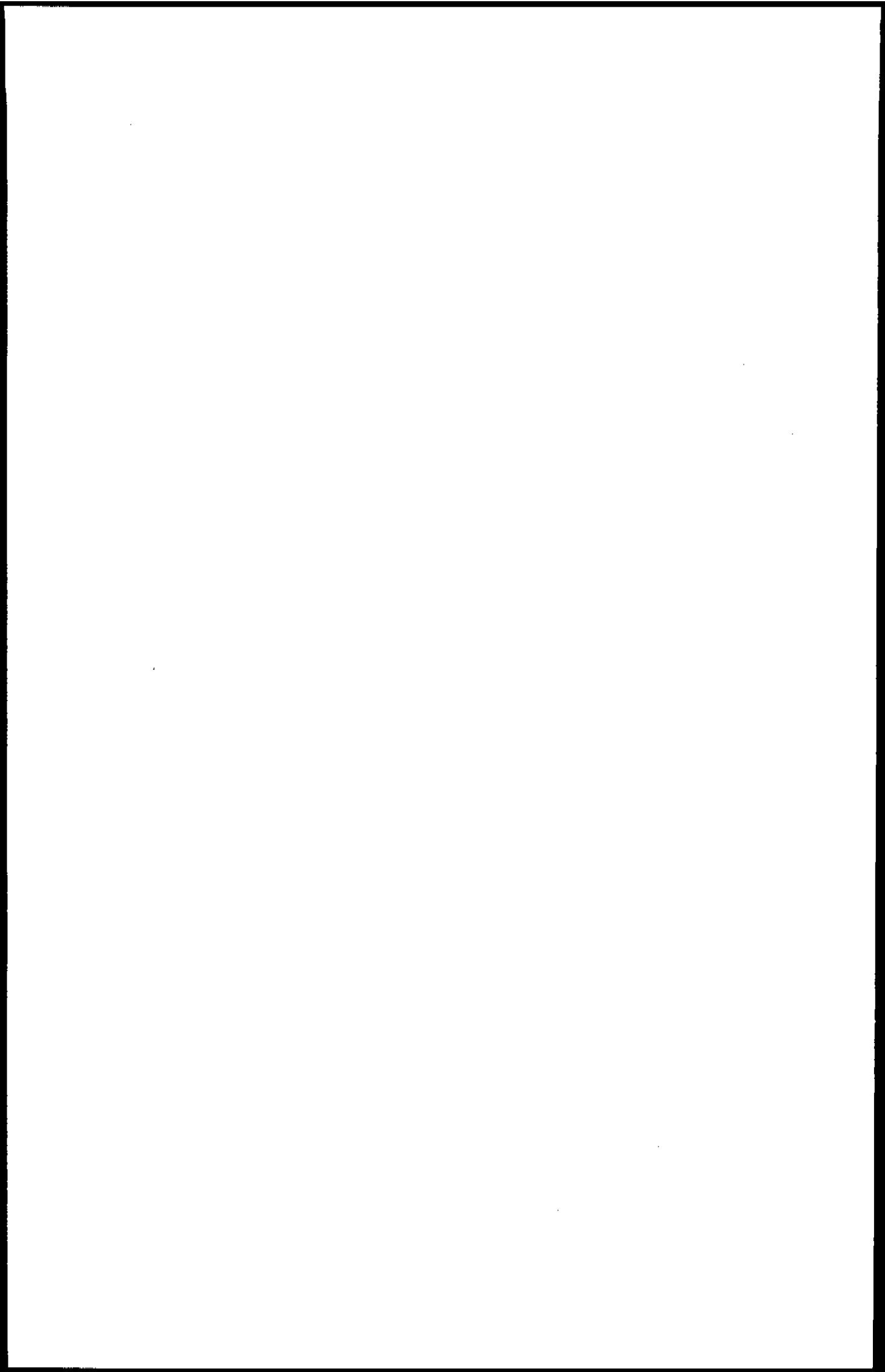
In sum, TDR identified a wide range of problems affecting Chagas disease, and created a mechanism to pursue its multiple objectives simultaneously. The Programme also recognized the strength of existing research into Chagas disease, especially among indigenous researchers living in the endemic countries in Latin America. TDR realized that it could best make contributions by coordinating those research activities.

EPICHA supervised research into vector control. Although scientists believed that it would be feasible to interrupt the transmission of *T. cruzi* in certain endemic areas by controlling domestic and peridomestic vectors with residual insecticides, they recognized that the key to making Chagas disease control programs sustainable would be to improve their operational and financial efficiency.

¹⁹ Division of Control of Tropical Disease, WHO. *Control of Tropical Diseases: Chagas Disease - A Disease Whose Days are Numbered*. Geneva. p. 8, 1996.

²⁰ Dias, JC. Chagas Disease Control in Brazil: Which Strategy after the Attack Phase? *Annales de la Société Belge de Médecine Tropicale*. 71(Suppl 1):75-86, 1991.

²¹ Schofield, CJ. Eradication of *Triatoma Infestans*: A New Regional Programme for Southern Latin America. *Annales de la Société Belge de Médecine Tropicale* 72 (Suppl. 1):69-70, 1992.



2. Activities and major players

For the purpose of analysis, this report divides the process of fumigant canister development into seven stages: discovery; testing; registration; production; pricing; distribution; and program implementation. A number of players were involved in the development of the fumigant canister: some of them interacted directly with TDR, and others acted independently. These major actors include:

- Centro de Investigaciones de Plagas e Insecticidas (CIPEIN-CITEFA/CONICET);
- other Argentine research institutions;
- the Argentine Ministry of Health and Chagas disease control agencies; and
- private companies in Argentina.

This section reviews TDR's activities at each stage of the development process, paying particular attention to the Programme's interactions with other players.

2.1 Discovery

The novelty of the fumigant canister's mechanism lies in the consecutive use of gaseous insecticides to produce a synergistic effect that kills more bugs than the use of each of the gases separately. A group of scientists led by Dr Eduardo Nicolas Zerba of the Centro de Investigaciones de Plagas e Insecticidas (CIPEIN) first observed this phenomenon in studies between 1974 and 1975 on the insecticidal effect of fumigants, especially methylbromide (CH_3Br) on *T. infestans*, the most important vector of Chagas disease in Argentina.²² These studies were supported by governmental institutions in Argentina, such as the National Council of Science and Technical Investigation, and the Secretariat of Science and Technology. The researchers first observed that CH_3Br and other insecticides were absorbed more efficiently through a respiratory route than by penetration through the cuticle of *T. infestans*. Their study also demonstrated an ovicidal effect of CH_3Br and SO_2 in gaseous form. Subsequent studies by Zerba et al. discovered that the increased respiratory rate produced by some insecticides, such as lindane and deltamethrin, enhanced the incorporation of other insecticide vapors, such as diethylchlorovinylphosphate (DDVP) and sulfurous anhydride, through the respiratory system, killing a larger number of *T. infestans* organisms than individual treatments.²³ These new research findings on the synergistic effects of insecticides in vapor phase resulted in the first fumigant cartridge. It was called CIPEIN PF-1, and contained lindane as the first active compound, and sulfurous anhydride as the second active component.

The collaborative relationship between CIPEIN and TDR began in the first year of TDR's activities for Chagas disease in 1978, and continues until today. As presented in Annex I, eight CIPEIN projects have been supported by TDR, with both basic research and applied research components. Initially,

²² Castro, JA. et al. Toxicity of Methyl Bromide and Other Gaseous Insecticides to *Triatoma Infestans*. *Acta Physiologica Latinoamericana* 26(2):106-14, 1976.

²³ Zerba, EN. et al. Sublethal Effects of Lindane in Vapor Phase on the Respiratory Activity of *Triatoma Infestans* (Hemiptera) As a Cause of Synergism in Fumigant. *Proceedings of the Fifth International Congress of Pesticide Chemistry (IUPAC)*, Kyoto, Japan, 1982.

TDR provided financial support to CIPEIN for basic research projects for 6 years.²⁴ Then, in 1984, TDR became financially involved in CIPEIN's applied research projects to develop the fumigant canister. At that point, the development process reached the stage of product testing and improvement, as described in the next section. It was hoped that CIPEIN's basic research would generate information to assist in the rational selection of insecticides against Chagas disease.

CIPEIN had a long history of research on Chagas disease prior to TDR's involvement. Between 1967 and 1974, CIPEIN focused its research on the synthesis of new triatomicide compounds and studies about reaction mechanisms. In 1974, CIPEIN began bioassays in *T. infestans*, including physiological studies about toxicokinetic steps on the vector treated with insecticides to search for novel synergism phenomena.²⁵

As shown in Table 1, CIPEIN received financial support from multiple sources for its basic and applied research related to the fumigant canister between 1978 and 1988. The fact that about three-quarters of the total funding was provided from Argentine sources reflects the country's significant commitment and its willingness to allocate resources for Chagas disease control.

In sum, during the stage of discovery, TDR made contributions in three forms:

- First, through its specialist committee of the Steering Committee on Epidemiology, Vector Biology and Control of Chagas Disease (EPICHA), TDR identified and encouraged a research opportunity that seemed to have the potential of improving operational and financial aspects of Chagas disease vector control programs. As stated by one TDR official, TDR's initial support to CIPEIN's basic studies in triatomine physiology and biochemistry "contributed to the establishment, quantification, and characterization of the phenomenon of synergism of the fumigant canister effect."²⁶
- Second, TDR provided the investigators who were developing the fumigant canister with opportunities for technical discussions with the broader network of Chagas disease researchers.
- Third, TDR financially supported the research process in a way that complemented and created legitimacy for the research support provided by national institutions.

²⁴ TDR projects ID No. 780385 and No. 810125.

²⁵ Picollo, M. et al. *Acta Bioquímica Clínica Latinoamericana* 10: 67, 1976. Zerba, EN. Development of New Insecticides and Synergistic Formulation of the Chagas' Disease Vector Control. *Revista Argentina de Microbiología*. 20(suppl): 25-31, 1988. Zerba, EN. Chemical Control of Chagas Disease Vectors. *Biomedical & Environmental Sciences*. 2(1): 24-29, 1989.

²⁶ Interview with a TDR official.

2.2 Product testing and improvement

With the discovery of a synergistic effect of certain insecticides in gaseous form, the development process of the fumigant canister moved to the second stage of product testing and improvement. Table 2 presents changes in the insecticide used in the fumigant canister, reflecting the results of laboratory and field tests. Although the composition of active compounds and the structure of the canister were modified over time, the basic mechanism of the fumigant canister remained largely unchanged. To deploy the canister, the user begins by lighting a fuse on its top, thereby causing combustion of the solid mixture without a flame, which produces gases containing the first compound. The heat produced during the first step is then transferred to the vial containing the second group of compounds, which is transformed into vapors and then dispersed by the combustion gases.

During the testing stage, the number of players increased substantially, and collaboration between them became important. First, in 1981, CIPEIN signed a contract with Medex-Omicron for development of an industrial prototype of fumigant canister for Chagas disease vector control. Medex-Omicron was an Argentine chemical company with experience in the production of insecticide fumigant mixtures. The collaboration between CIPEIN and Medex-Omicron grew out of an informal relationship that began in 1980 between the researchers and professional staff of the two organizations.²⁷ In 1982, the second version of the fumigant canister, CIPEIN PF-2, was developed by Medex-Omicron, which contained lindane and diethylchlorovinylphosphate (DDVP) as active compounds. A field test of CIPEIN PF-2 was conducted in Villa Silipica and Villa Giménez, in the Province of Santiago del Estero, Argentina, in 1982, and showed 100 per cent initial efficacy against *T. infestans*. The test also pointed out, however, that the reinfestation rate of *T. infestans* 30 days after the treatment was very high.

A second group of collaborators included other Argentine research institutions and Chagas disease control agencies. For example, when the third version of the fumigant canister (CIPEIN PF-3) was developed in 1983, by adding fenitrothion for better ovicidal and residual effects, the Argentine Secretariat of Health funded the development through the Dr Mario Fatała Chaben Institute (INDEICH), while TDR supported its laboratory study and field trial.²⁸ The Secretariat of Health of Argentina and the University of Córdoba also participated in the field test in Villa Giménez, Province of Santiago del Estero. This field test showed that there was no reinfestation 220 days after treatment using CIPEIN PF-3 in houses that were treated indoors with the fumigant canister and outdoors with hexachlorohexane (HCH). The reinfestation rate was 14.3% for houses treated both indoors and outdoors with HCH.²⁹ The study showed no adverse signs for the inhabitants of the dwelling.³⁰ Thus, the trial suggested a promising prospect for the fumigant canister as a new, simple, and effective tool

²⁷ Personal communication from Dr E.N. Zerba, October 4, 1996.

²⁸ TDR project ID No. 830213.

²⁹ Zerba, EN. et al. *Chagas*. 5:10-28, 1988.

³⁰ Zerba, EN. Development of New Insecticides and Synergistic Formulation of the Chagas' Disease Vector Control. *Revista Argentina de Microbiología*. 20(suppl): 25-31, 1988.

for indoor treatment against *T. infestans*. The tool would allow a decentralized control strategy during the surveillance phase, in which households and communities could actively participate in vector control through the use of the fumigant canister.

- Another longitudinal field study by Dr E. Segura of INDEICH, under the auspices of the Argentine Secretariat of Health, confirmed the effectiveness of the new tool. The study was conducted in the Province of Santiago del Estero in cooperation with the Chagas National Control Program (ChNCP: a disease-specific national control agency under the National Epidemiology Directorate), with TDR's financial support between 1985 and 1989. This study demonstrated two key points.³¹ First, a community (or "horizontal") approach to Chagas disease vector control using new tools, such as triatomine sensor boxes and the fumigant canister, and the involvement of the local population at the surveillance phase, was just as effective in interrupting the transmission of *T. cruzi* as a conventional "vertically" organized approach with a heavy reliance on professional staff for vigilance and spraying activities.³²
- Second, the study provided data showing that the use of the fumigant canister would be economically beneficial for control programs. The cost of surveillance activities with a horizontal approach using the fumigant canister was US\$ 4.70 per house per year, while the cost of a vertical program was US\$ 22.30 per house per year.³³

The next version of the fumigant canister, CIPEIN PF-4, was developed as a result of further modifications in the internal design of the canister that resulted from research findings by CIPEIN. CIPEIN PF-4 contained a glass flask so that the heat produced by the combustion could be transmitted more effectively to the insecticides that were located in the flask, in turn promoting vaporization.

The internal design of the canister was further modified for industrial production when the first industrial model of the fumigant canister (CIPEIN PF-5) was developed by CIPEIN in collaboration with an Argentine company, Aguvac. Lindane and fenitrothion were replaced by two new pyrethroid insecticides, deltamethrin and cypermethrin, due to environmental concerns. After field tests in La Rioja and Córdoba, CIPEIN PF-5 was introduced to the market in 1988 under the trade name of "Agufog®."

These laboratory and field studies produced useful information that expanded the discovery of the basic mechanism of the fumigant canister to a product that was suitable for use in vector control. The studies also demonstrated that the fumigant canister was an effective tool that could expand a community's participation in vector control because it was suitable for a decentralized approach.

³¹ TDR project ID No. 840362.

³² Chuit, R. et al. Result of a First Step Toward Community-Based Surveillance of Transmission of Chagas' Disease with Appropriate Technology in Rural Areas. *American Journal of Medicine and Hygiene*. 46(6):444-450, 1992.

³³ Segura, El. et al. *Final Report of TDR project ID No. 840362*. April 5, 1990.

TDR's contributions at this stage were three-fold:

- First, TDR's continuous support to the project demonstrated the significance and the relevance of the fumigant canister innovation for Chagas disease control strategy, and created an environment that encouraged the interest of other research institutions and control agencies in this innovation.
- Second, the structure of the Scientific Working Group and its subcommittee EPICHA provided investigators working on the fumigant canister with opportunities to exchange information with other Chagas disease researchers. The development of the canister also began to foster a collaborative relationship between basic researchers and vector-control professionals in Argentina.
- Third, TDR maintained its financial contribution for the fumigant canister development, and also allowed the innovators to pursue links with the commercial sector.

2.3 Registration

In Argentina, there are two types of registration associated with the fumigant canister: patent registration; and product registration as an insecticide. In September 1985, CIPEIN submitted an application for a patent for the fumigant canister in Argentina and received patent protection until April 18, 2011.³⁴ The use of the fumigant canister (CIPEIN PF-5) as an insecticide was first approved by the Ministry of Health of Argentina in September 1988.³⁵ The new generation of the fumigant canister, CIPEIN PF-6, was also approved by the Ministry of Health in 1994.

Outside of Argentina, the fumigant canister is also registered in Bolivia, and is in the process of registration in Paraguay. It is likely that Chemotecnica Sintyal, the company that currently produces the fumigant canister, will seek product registrations in other Latin American countries, since the company is strongly interested in expanding the market for the fumigant canister outside Argentina.³⁶

Registration processes have been handled by companies and CIPEIN, and TDR was not involved in any of these applications.

2.4 Production

In 1984, CIPEIN organized a meeting with major companies producing insecticides in Argentina in order to explore partners in the private sector for the industrial production of the fumigant canister. One company, Aguvac, showed interest in the project, and a contract was signed between CIPEIN and Aguvac in April 1985 for the industrial production of the fumigant canister (the contract was extended in March 1986.) Under this contract, the first generation of the fumigant canister for industrial production was developed (CIPEIN PF-5), which was introduced to the market in 1988 under the trade name of "Agufog®." Aguvac changed its corporate organization subsequently, and we could not trace

³⁴ Argentine patent 248872 "Un Dispositivo Fumígeno Insecticida."

³⁵ República Argentina Ministerio de Salud y Acción Social, Secretaria de Salud. *Certificado Producto Insecticida. (Certificado No. 10142).*

³⁶ Communication from Chemotecnica Sintyal, November 27, 1996.

contacts to obtain further information. However, data from TDR indicate that the government of Argentina purchased about 170,000 units of fumigant canisters that were produced by Aguvac in 1991 and 1992. (Table 3)

In 1994, the agreement between CIPEIN and Aguvac was terminated, and CIPEIN transferred the production license of the canister to Chemotecnica Sintyal, another Argentine company in the agrochemical and pharmaceutical business. In the same year, CIPEIN and Sintyal developed the latest version of the canister (CIPEIN PF-6), which is currently sold in Argentina under the trade name "Musal®". In this version, deltamethrin was replaced by another new pyrethroid insecticide, permethrin. In addition, CIPEIN PF-6 contains the *cis* isomer of cypermethrin (β -cypermethrin) which showed a stronger triatomicide effect than the *trans* isomer.³⁷ The inclusion of a thermal protector prevents the decomposition of pyrethroid components during combustion, and thus the stability of the insecticidal effect was improved.³⁸

All active compounds for the fumigant canisters that are currently in use (i.e., CIPEIN PF-5 Plusefec® and PF-6 "Musal®") are produced in Argentina by Chemotecnica Sintyal, except β -cypermethrin, which is imported by Sintyal from Hungary under an agreement that gives the company the right to exclusive sales in the public health market in Latin America. We were unable to obtain further information about the production of the fumigant canister by Sintyal, so that the annual production volume and its growth rate are unknown.

Although Sintyal is the only company that has a legal right to produce and sell the fumigant canister, two Argentine companies are reported to be producing fumigant canisters similar to CIPEIN PF-5, but of lesser quality, without an agreement with CIPEIN, thus violating the patent protection law.

TDR has not been involved in any of the negotiations between CIPEIN and private companies for the production of the fumigant canister in Argentina.

2.5 Pricing

As the development process was progressing in mid-1986, the price of the fumigant canister became an issue for TDR. Discussions took place between CIPEIN researchers and the Programme, with some consultations with the Office of Legal Counsel of WHO. TDR did not directly negotiate with Aguvac, the first private manufacturer of the canister. The major issue was how much royalty should be given to CIPEIN, as the inventor, from sales of the fumigant canister. CIPEIN stated that it expected to receive a royalty payment from sales of the fumigant canister, which could be reinvested for further research on Chagas disease.³⁹

³⁷ Zerba, EN. et al. Final Report of TDR Project ID No. 910300. March 30, 1994.

³⁸ Alzogaray, RA. and Zerba, EN. Temperature Effect on the Insecticidal Activity of Pyrethroid on *Triatoma Infestans*. *Comp. Biochem. Physiology*. 104C(3):485-488, 1993.

³⁹ Minutes of the meeting between WHO and CIPEIN on July 11, 1986. (TDR File at WHO, Geneva)

TDR explained WHO's general policy on the commercial exploitation of research work supported by WHO funding. According to this policy, the following objectives should be pursued in this order of priority:

- The general availability of products;
- The availability of the product to the public health sector on preferential terms;
- The grant to each party of additional benefits, including royalties, taking account of the relative value of each party's financial, intellectual and other contributions to the research.⁴⁰

Two factors affected the negotiations. First, it was not known in 1986 whether a private market existed for the fumigant canister. Second, TDR was not the sole funder of the project, and thus was not in a strong position to determine pricing decisions. TDR expressed the view that if there were a private market, then a two-tier price system should be established, so that the fumigant canister would be sold to the public health sector at the lowest possible reasonable price, while "the private sector price would be the sole concern of the enterprise which was expected to make the majority of its financial benefit from such sales."⁴¹ TDR also stated that a royalty payment could then be obtained from the private sector sales. TDR further stated that if only a limited private market existed for the product, then the royalty payment from the public sector sales should be reduced by taking into account the relative importance of TDR's contribution to the project. TDR proposed that TDR's overall contribution represented 20 per cent of the project; this figure resulted from doubling the proportion of TDR's financial contribution (10 per cent) in consideration of TDR's "catalytic element both in terms of enabling the work to progress and in terms of attracting additional funding from the Government."⁴²

In December 1987, a contract was signed between CIPEIN and Aguvac for commercial production of the fumigant canister. Initially, Aguvac decided not to sell the canister in the private market, but to produce the fumigant canister only for the government sector: namely, the Ministry of Health, local offices of vector control, and TDR (for the purpose of field research). This decision by Aguvac partially satisfied TDR's concern that the public health sector should have priority access to the fumigant canisters. However, the decision also resulted in a royalty payment to CIPEIN from public-sector sales. TDR's suggested reduced royalty payment was not included in the agreement between CIPEIN and Aguvac.⁴³ We were unable to determine the level of the royalty payment or the total amount of royalties received to date by CIPEIN from public sales of the fumigant canister.

According to one official of the Argentine Ministry of Health, the public sector purchase price of the fumigant canister declined significantly from the initial level of US\$ 5-6 in 1986 to the current level of US\$ 2.20 per canister.⁴⁴ However, we were unable to determine the retail price in the private

⁴⁰ Letter from Director of TDR to Dr E.N. Zerba dated December 15, 1986. (TDR File at WHO, Geneva)

⁴¹ Letter from Director of TDR to Dr E.N. Zerba dated December 15, 1986. (TDR File at WHO, Geneva)

⁴² Letter from Director of TDR to Dr E.N. Zerba dated December 15, 1986. (TDR File at WHO, Geneva)

⁴³ Letter from Dr Zerba to Director of TDR, dated February 29, 1988. (TDR File at WHO, Geneva)

⁴⁴ Interview with an official of the Ministry of Health in Argentina on October 2, 1996.

market, or to find data on total private sales, although we understand Aguvac did decided to sell the fumigant canister in the private market in Argentina.

In sum, TDR's role during the pricing stage was to ensure that the product was made widely available for use in the public sector at a low price, thereby pursuing its main objective for the project. TDR attempted to fulfil this role by presenting a set of guidelines for the pricing process. Although some of TDR's recommendations were reflected in the pricing discussions, the extent to which the Programme influenced the decisions was limited, because it was not in a dominant position in the negotiations, especially compared to the government of Argentina, which had invested more funds in the project than TDR.

2.6 Distribution

At present, the fumigant canister for Chagas disease vector control is available only in Argentina. Procurement and distribution of the canister are arranged between purchasers and the manufacturer in both public and private sectors. In 1991, the Ministry of Health of Argentina adopted the fumigant canister in its national Chagas disease control strategy, and began purchasing the canister. Since then, the government of Argentina has been the most important bulk purchaser of the fumigant canister with a total of 495,000 canisters from 1991 to 1995, for a total value of US\$ 1,237,500 (estimated at US\$ 2.50 average per canister). Table 3 presents the quantity and value of fumigant canisters purchased by the government of Argentina since 1991.

The Argentine National Epidemiology Directorate purchases the fumigant canisters, and then distributes them to state agencies and to municipalities through the Chagas National Control Program (ChNCP: a disease-specific national control agency under the National Epidemiology Directorate). TDR has not been involved in any activities related to the distribution of fumigant canisters in Argentina.

2.7 Program implementation

While the government of Argentina is implementing its Chagas disease control program using the fumigant canister, TDR is organizing multi-country studies of new tools for Chagas disease control that include tests of the canister. In October 1989, TDR organized a meeting in Montevideo, Uruguay, to establish a standard protocol for these studies. The new tools include insecticide paint, fumigant canister, and triatomine detection box. The studies will evaluate these control tools in three aspects: entomological transmission, social acceptability, and economic impact.⁴⁵ Studies are being conducted in Argentina, Bolivia, Chile, Honduras, Nicaragua, and Paraguay. As of June 1996, TDR had provided US\$ 382,000 for the studies. These multi-country studies are intended to assess the use of fumigant canisters in Chagas disease control programs under different entomological, socio-cultural, and ecological settings. The studies are also creating opportunities to introduce fumigant canisters to Chagas disease researchers and control personnel outside Argentina.

⁴⁵ WHO. *Protocolo Estandar para el Ensayo de Nuevas Estrategias de Control de Vectores de la Enfermedad de Chagas*. 1989. (TDR/CHA/URU/89.3)

3. Conclusions

This report reviewed seven stages in the process of fumigant canister development and the involvement of major actors, in order to analyze the contributions made by TDR. Before discussing our findings about TDR's role, we briefly note three impacts that fumigant canisters are expected to have on Chagas disease control strategy:

First, the canister is expected to improve the overall efficiency of vector control programs by preventing reinfestation after initial spraying. Originally, the fumigant canister was intended to be used in the "attack" phase, but it was found that the fumigant canister was not as effective as house-to-house spraying; therefore, the canister was adopted during the "surveillance" phase. To interrupt the transmission of Chagas disease, control programs must prevent sprayed houses from becoming reinfested by vector insects after the attack phase, during the surveillance phase. However, the surveillance phase is the longest of the three phases of control activities, and it is often difficult to maintain the political and financial commitment at the same level as during the attack phase, which is shorter and more visible.⁴⁶ The fumigant canister can help to solve these problems by allowing the surveillance phase to be integrated into the activities of primary health care. Thus, the fumigant canister is expected to make the surveillance phase of vector control programs more sustainable in areas where domiciliary vectors are the major targets, so improving the overall efficiency of the programs.

Second, the use of fumigant canisters is expected to reduce the financial costs of vector control programs. Few studies have been conducted (beyond the one by Segura et al. mentioned above⁴⁷) to indicate the precise reduction in costs of control programs through the use of fumigant canisters instead of conventional surveillance activities by professionals. But it is known that the unit cost of control activities per house during the surveillance phase is higher than that during the attack phase, since fewer houses are targeted in the surveillance phase. In Argentina, the unit cost of the surveillance phase is estimated at US\$ 60-80 per house, while it is US\$ 40-45 in the attack phase.⁴⁸ A cost-effectiveness study by Schofield and Dias suggested that the fixed costs of vector control programs for Chagas disease (such as salary for spray teams, administration and overhead) account for nearly two-thirds of the house spraying expenses.⁴⁹

Third, the fumigant canister provides a new tool that can create opportunities for wider participation of the local population in Chagas disease control activities. In vertically organized control programs,

⁴⁶ Dias, JCP. Chagas Disease Control in Brazil: Which Strategy after the Attack Phase? *Annales de la Société Belge de Médecine Tropicale*. 71(Suppl 1):75-86, 1991.

⁴⁷ Segura, EL. et al. *Final Report of TDR project ID No. 840362*. April 5, 1990.

⁴⁸ Interview with an official of the Ministry of Health in Argentina on October 2, 1996.

⁴⁹ Schofield, CJ. and Dias, JCP. A Cost-Benefit Analysis of Chagas Disease Control. *Memorias do Instituto Oswaldo Cruz*. 86(3):285-95, 1991.

communities in endemic areas are mostly spectators.⁵⁰ People with a high risk of Chagas disease live in historical and economic conditions that make it difficult to change their sense of helplessness and involve them in control activities. Because of its simple operation, however, the fumigant canister offers opportunities for the local population to adopt a more active role in controlling Chagas disease.

Finally, it is worth noting that it is difficult to specify how much of the decline in the prevalence of Chagas disease in recent years can be attributed directly to the fumigant canister. This is because the canister is used as one element of an integrated vector control program. Data from the Argentine National Chagas Disease Control Program indicate progress achieved along several dimensions in recent years: the proportion of houses infested by the vector was reduced by an average of 50.5 per cent between 1982 and 1994 (ranging from 30.9 per cent to 94.4 per cent depending on provinces); reductions of 81.0 per cent, 46.3 per cent and 24.3 per cent in the number of infected cases are estimated respectively in the age groups under 18 years, from 18 to 35 years, and from 35 to 50 years old, compared to the number of infections that might have been expected in the absence of control activities.⁵¹ The extensive use of the fumigant canister by ChNCP since 1991 probably contributed to these achievements, but we cannot isolate the direct impact of the canister use from the overall outcome of the intensified vector control programs in Argentina during this period.

Table 4 summarizes the results of our analysis of TDR's contributions, as well as the involvement of other major actors, at each stage of the fumigant canister development process. TDR made its most significant contributions during the stages of discovery, testing, and program implementation. TDR also played a moderate role in pricing. TDR's activities were negligible in the processes of registration, production, and distribution. Considering the mandate of TDR to promote research and development of new tools for the control of tropical diseases, this pattern of TDR's activities for fumigant canister development suggests that TDR's involvement was guided by, and was consistent with, its mandate.

Our analysis identified four forms of contributions by TDR to the development of the fumigant canister:

- TDR's first contribution was the financial support that it provided to the projects. As noted above, the projects for fumigant canister development received financial support from multiple sources, including TDR. The significance of TDR's financial support lay not primarily in its amount, but in its continuity. TDR identified a group of researchers with technical capacity and scientific interest in a subject that was compatible with TDR's priorities. The Programme then maintained its support for basic research and for applied research by CIPEIN, providing a total of US\$ 175,000 over 11 years, for 27% of all research funds for the fumigant canister in this period.

⁵⁰ Zerba, EN. et al. *Application for Scientific Working Group Collaborative Research Project: Experimental Programme for Chemical Control of Chagas' Disease Vectors with Community Participation* (TDR Project ID No. 830213). April 30, 1983.

⁵¹ TDR. *Chagas Disease - Progress Towards Elimination of Transmission, Argentina. WHO Weekly Epidemiology Record.* 71:12-15, 1996.

- TDR's second contribution was the legitimacy it provided for the innovation and for the innovators. Our interviews suggest that TDR's continuous support to the canister project enhanced the credibility of this new tool among other major players in Argentina in terms of its scientific significance and its relevance to Chagas disease control. This form of contribution seems to have been particularly important for the decision by the government of Argentina to adopt the fumigant canister in the national control program.
- TDR's third contribution was to provide organizational support to the investigators of the project, and thereby facilitate the development process. The mechanism of collaboration between TDR and CIPEIN for the fumigant canister included regular reporting to and consultation with EPICHA, and participation in meetings organized by TDR. These activities provided the investigators with a forum for exchanging information and experiences with other researchers in Latin America. The development process also fostered a collaborative relationship between basic researchers and disease control professionals in Argentina, who otherwise had limited opportunities to know each other's experiences and expertise.
- Fourth, TDR contributed by disseminating information about the innovation to the broader community of Chagas disease researchers, and by promoting the expansion of the project beyond Argentina through multi-country field trials with a common protocol. The results of these ongoing trials will show whether the fumigant canister is effective in different ecological situations and for different vectors in other parts of Latin America.

Our analysis also identified three external factors that significantly fostered TDR's contributions:

- First, there was a growing political momentum to fight Chagas disease in Latin America since the late 1970s. Between 1975 and 1981, Brazil conducted a large-scale seroepidemiological survey on Chagas disease. In 1979, the International Congress on Chagas Disease was organized in Rio de Janeiro, Brazil, which was followed by Annual Meetings on Basic Research in Chagas Disease in Caxambu, Brazil. In the early 1980s, Brazil and Argentina intensified vector control activities. In 1991, Argentina, Brazil, Bolivia, Chile, Paraguay, and Uruguay launched the "Initiative for the Elimination of Chagas Disease by Southern Cone Countries." TDR began its activities for Chagas disease in 1978 in the midst of these events, and TDR helped keep this momentum growing. As stated in the Programme's report, the "development of new tools for vector control, such as insecticide paints and fumigant canister, made it possible to consider elimination of the disease."⁵² At the same time, however, TDR benefited greatly from this positive environment.
- Second, there were technically competent and innovative researchers and institutions in Latin America who were interested in, and committed to, the development of new tools for Chagas disease control. This is an unusual situation for product development for tropical diseases. Often, there is a geographical discrepancy between the needs for disease control in endemic countries and the technical capacity in non-endemic developed countries.

⁵² TDR. *Tropical Disease Research: Progress 1991-92, Eleventh Programme Report* p.70.

- Third, there were competent industrial partners in Argentina, and they cooperated with researchers to transform the innovative research into a tangible product. This is another strength of the Latin American region.

This report presents the results of our analysis of TDR's involvement in the process of fumigant canister development through August 1996. The analysis indicates that TDR played an important role in identifying the potential of innovative research activities and in helping develop a new product to address operational problems in Chagas disease vector control. One strength of TDR derives from its wide network of individual researchers in both endemic countries and non-endemic developed countries. The TDR committees used this network of scientists to assess and articulate priority areas, and to coordinate research activities in order to achieve TDR's overall objectives in the area of Chagas disease.

Whether the fumigant canister will be used in other countries for Chagas disease control remains to be seen. If the results of the ongoing multi-country trial indicate the usefulness of this innovative tool in other endemic countries outside Argentina, then TDR will need to assess its role in facilitating further proliferation. In order to promote the adoption of the fumigant canister in countries outside Argentina, additional industrial partners may be necessary, and negotiations for concessional prices and distribution mechanisms may be needed. However, our analysis shows that TDR has not been very active in production and distribution processes. Given that TDR's mandate emphasizes the promotion of research and training activities, it may be expected that TDR's role gradually diminishes during the production and distribution stages. If TDR wants to assure maximum benefits from the fumigant canister and from TDR's resources invested in the project, then a new organizational mechanism may be needed to promote the application of the fumigant canister in other Latin American countries.

ANNEX 1

LIST OF TABLES

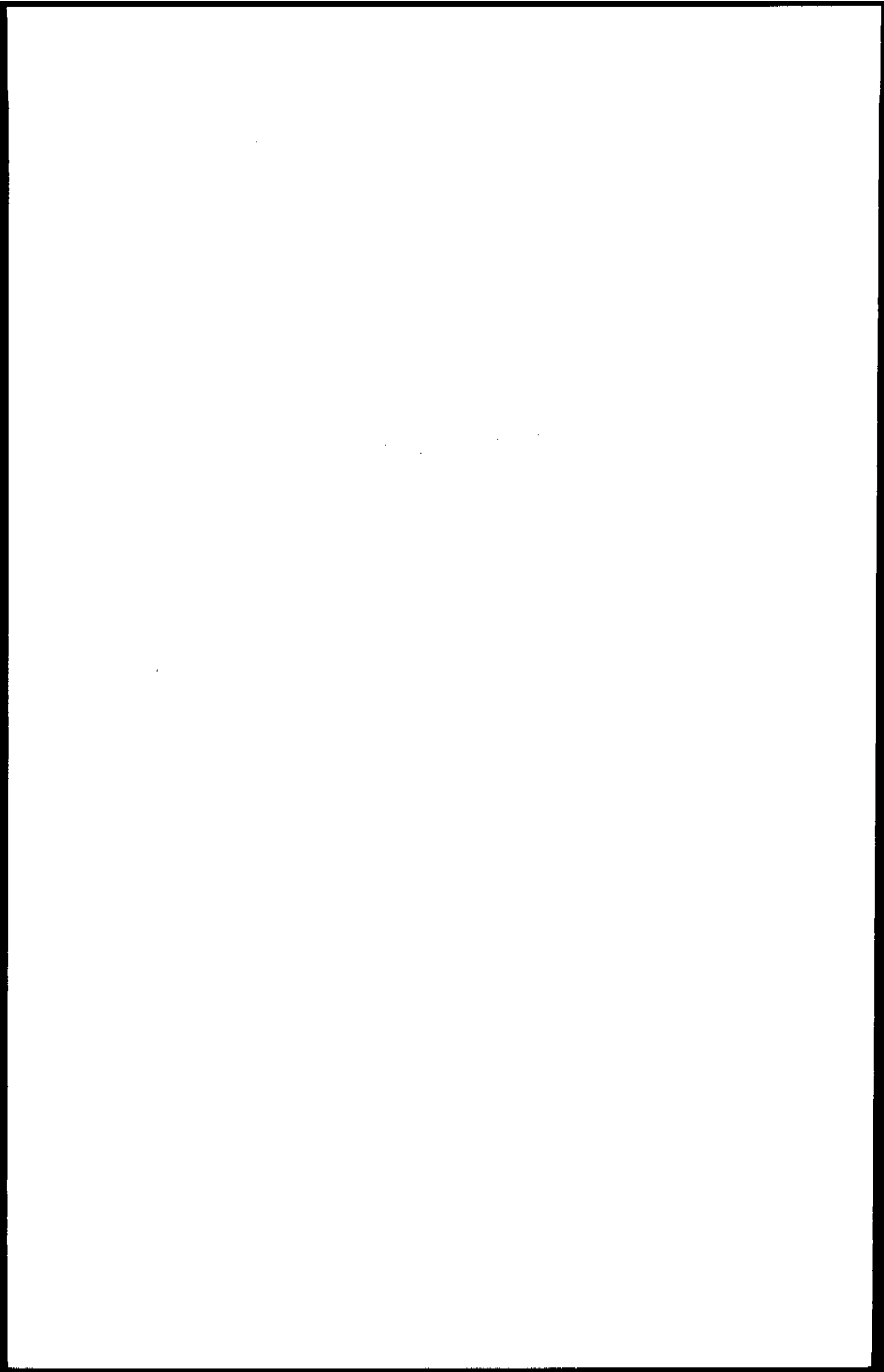


Table 1
**Funding for Basic and Applied Research Leading to the Development of
Fumigant Canister for Triatomin Control by CIPEIN (1978-1988)**

Year	(US \$)			
	National Secretariat of Public Health	National Research Council	TDR	TOTAL
1978	15,000	30,000	30,500	75,500
1979	30,000	25,000	4,500	59,500
1980	60,000	42,000	6,500	108,500
1981	25,000	35,000	15,000	75,000
1982	---	28,000	14,000	42,000
1983	20,000	23,000	14,000	57,000
1984	10,000	21,000	13,000	44,000
1985	---	25,000	23,500	48,500
1986	---	29,000	21,500	50,500
1987	---	26,000	19,500	45,500
1988	---	32,000	13,000	45,000
TOTAL	160,000 (25%)	316,000 (48%)	175,000 (27%)	651,000 (100%)

Source: TDR

Table 2
Active Ingredients of Fumigant Canisters

Model	1st compound	Other compounds	Note
PF-1	Lindane	Sulfurous anhydride	
PF-2	Lindane	Diethylchlorovinyl- phosphate (DDVP)	DDVP has rapid triatomicidal action, but has no ovicidal effect, nor has residual effect.
PF-3	Lindane	DDVP + Fenitrothion	Fenitrothion was added in order to strengthen ovicide effect and residual effect.
PF-4	Lindane	DDVP + Fenitrothion	The internal design of the canister was modified to improve the heat transmission.
PF-5	Deltamethrin	DDVP + Cypermethrine	Due to environmental concerns, lindane and fenitrothion were replaced by deltamethrin and cypermethrine. Also a new internal design of canister was adopted for industrial production.
PF-6	β -Cypermethrine	DDVP + Permethrin	The new insecticide formulation improved the stability of active compounds due to thermal decomposition.

Table 3
Quantity of Fumigant Canisters Purchased
by the Government of Argentina

Year	Number of fumigant canisters purchased	Commercial value (US\$)
1991	108,000	270,000
1992	60,000	150,000
1993	n.d.	n.d.
1994	140,000	350,000
1995	187,000	467,500
Total	495,000	1,237,500

[Note] Calculation is based on the unit price of one canister as US\$ 2.50
n.d.: no data available

(Source: TDR)

Table 4
Contributions of Major Actors to the Development of Fumigant Canister

	TDR	CIPEIN	<i>Other Argentine Research Institutions</i>	<i>Argentine Chagas Disease Control Agencies</i>	<i>Local Industry in Argentina</i>
<i>Discovery</i>	++	++	+	-	-
<i>Product Testing & Improvement</i>	++	++	++	++	++
<i>Registration</i>	-	++	-	-	++
<i>Production</i>	-	++	-	-	++
<i>Pricing</i>	+	++	-	-	++
<i>Distribution</i>	-	-	-	++	++
<i>Program Implementation</i>	+	++	+	++	+

Note: ++ Significant contribution
+ Moderate contribution
- Negligible contribution

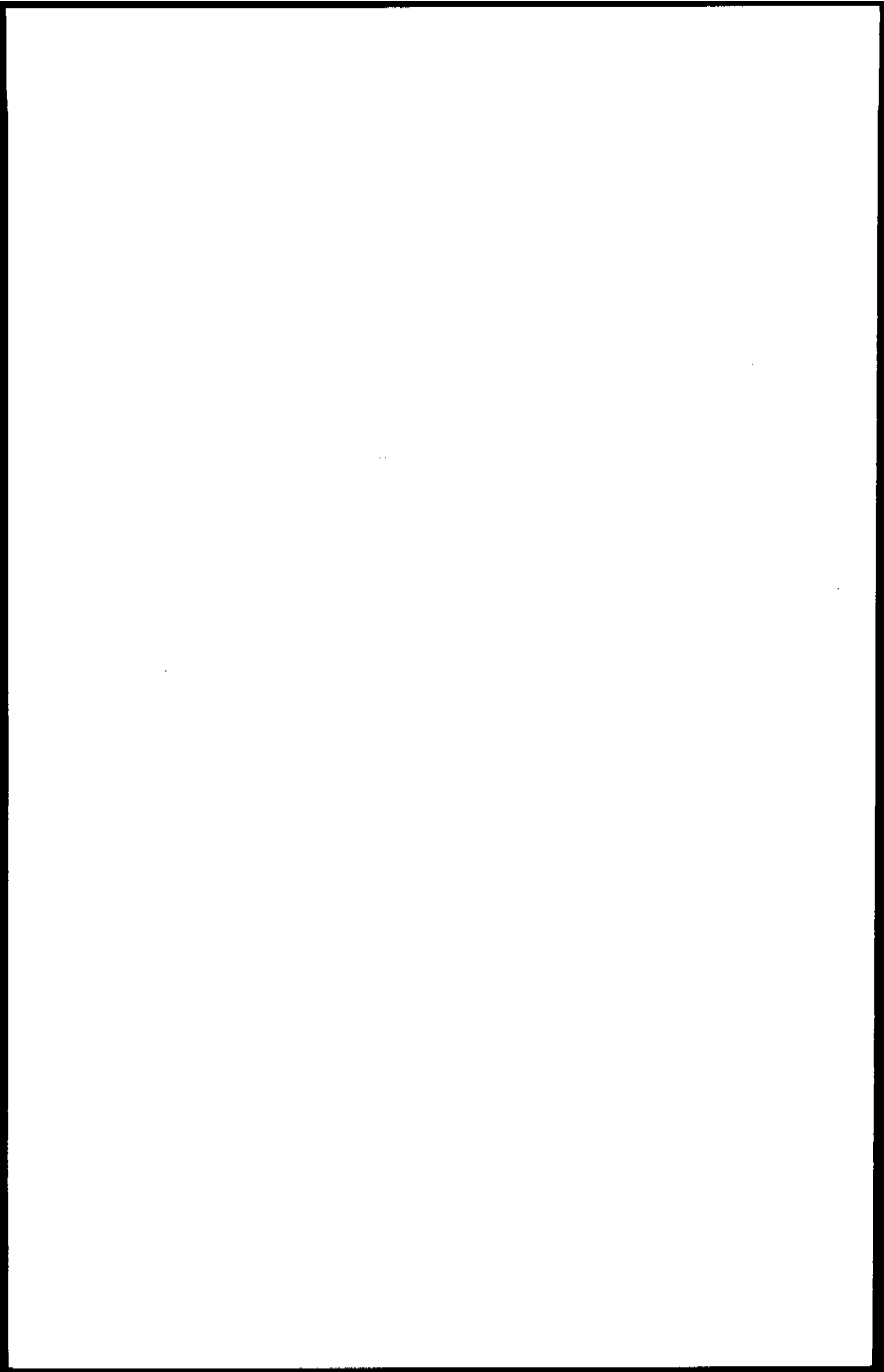
Figure 1. TDR Funded Research Projects for Development of Fumigant Canister

Year	Basic Research Component	Applied Research Component	
1978	TDR 780385 (CIPEIN) Relationship between structure of organophosphorous compounds and insecticide action against <i>T. infestans</i>		
1979			
1980			
1981			
1982	TDR 810125 (CIPEIN) (1) Search for new synergists (2) Examination of activation metabolism of phosphorothioates (3) Evaluation of pyrethroids & new thiodicarbamates (4) Development of resistant strain of <i>T. infestans</i>		
1983			
1984			
1985			
1985	TDR 84244 (CIPEIN) (1) Synergistic mechanism of organophosphorous insecticides (2) Metabolism of pyrethroids in <i>T. infestans</i> for synergism possibilities (3) Esterase of <i>T. infestans</i> to study variation in insecticide action with the age of vectors (4) Biochemical causes of malathion resistance in <i>T. infestans</i>	TDR 830213 (CIPEIN) (1) Improvement of CIPEIN PF-3 (2) Search for insecticide formulation with a long residual activity (3) Evaluation of control methodology (4) Organization of control maintenance activities with community participation using the fumigant can CIPEIN PF-3	TDR 840362 (INDIE) Development of method for the surveillance of transmission of Chagas disease in rural areas based on the use of appropriate technology
1986			
1987			
1988			
1989	TDR 870279 (CIPEIN) (1) Antifeedant effect of SH reagents and delayed mortality of vectors (2) Inhibition of GSH biosynthesis and inhibition of glutathione transferases (3) Triatomicide effect of phosphorodithioates derivatives of malcamic ester	TDR 860184 (CIPEIN) (1) Evaluation of fumigant can in vigilance activities (2) Development and evaluation of fumigant tablet as flush out agent (3) Development of insecticide-polyethylene film (4) Evaluation of formulation	
1990			
1991	TDR 910300 (CIPEIN) (1) Systematic lab studies of pyrethroids on variables affecting the triatomicide effect	(2) Pyrethroid impregnated fabrics (PIF)	
1992			
1993			
1994	TDR 940246 (CIPEIN) (1) Field studies of PIF (2) Development of new fumigant canister and pyrethroid tablet	(3) Design of detection and monitoring method for pyrethroid resistance in <i>T. infestans</i>	
1995			
1996			

Note: This chart presents all TDR projects (1978-1996) that provided financial support for development of the fumigant canister.
 Source: TDR

ANNEX 2

METHODOLOGY



Methodology

Objectives of the Study

The overall purpose of the study was to review TDR's contributions in the development of fumigant canisters for the vector control of Chagas disease.

The broad objective of the study was to assist in evaluating TDR's past actions, in order to shape decisions about TDR's future role and strategies for product development for tropical diseases. For each product, the study sought to describe and evaluate:

- Specific actions taken by TDR;
- Major consequences of TDR's actions for product development and for disease control programs; and
- Strategies and conditions that fostered, or hindered, successful outcomes of product development.

Methods of the Study

The analysis of the processes of product development was based on the results of a major study of the development of praziquantel for treatment of schistosomiasis, previously carried out by the principal investigator (Reich et al., 1996). That study examined the roles of four major actors (international agencies, developing country governments, private suppliers including non-governmental organizations, and pharmaceutical producers) across a series of specific processes in product development. Those processes were adapted for the current TDR study into seven stages:

- discovery,
- clinical trials,
- registration,
- production,
- pricing,
- distribution, and
- program implementation.

For each stage in the product development cycle, this study sought to describe and assess TDR's role and actions, and particularly how TDR interacted with other major actors involved in product development. One of the major findings of the praziquantel study was the importance of cross-organizational relationships. The development of effective products for tropical diseases requires multiple organizations working together. This study sought to examine how TDR managed cross-organizational relationships for the three selected products.

This study's analysis was guided by five main questions:

- What were the disease control problems that TDR sought to resolve through its program for each product?
- What were the major activities carried out by TDR for each product?
- How did TDR's activities affect product development at each stage (including discovery, clinical trials, registration, production, pricing, distribution, and program implementation)?
- What were the major contributions made by TDR for each product?
- In what ways could TDR have improved its contributions for each product?

To address these questions, information on TDR's activities were collected through: a review of the published literature; on-site examination of unpublished documents and memoranda at TDR; and interviews with key persons at WHO and at other organizations involved with the development of each product. Throughout, the study attempted to collect different perspectives on TDR's role and activities, in order to provide a more balanced viewpoint on TDR's contributions and limitations. Table 1 presents the kinds of information sought at each stage in the product development cycle, and the data sources used (in addition to interviews) for the analysis of TDR's involvement.

Based on the data collected, the study used qualitative and semi-quantitative methods to assess TDR's involvement in each stage of product development. In the qualitative methods, the information collected was presented in a descriptive text, using a common structure for each study. The first section presented the disease control 'problem' as perceived and defined by TDR in the 1970s. The second section presented the activities of the major players, with a focus on TDR, for each of the seven stages of product development. The final section then presented a series of conclusions and themes drawn from the case study.

The study also includes a table that assesses the contributions of the major actors at each stage of product development. Three 'levels' of contribution were used in the assessment: negligible (-), moderate (+), and significant (++). This assessment necessarily required some judgment on the part of the researchers. The category of "negligible" was defined as no activity during a specific stage, or no activity that had an impact on the course of events. In most cases, this assessment was fairly clear from the data collected. The distinction between "moderate" and "significant" contribution required more judgment. A contribution was defined as "significant" if it involved substantial resources and if it also resulted in a major impact on the course of events. Actions that did not meet these two criteria were considered to make "moderate" contributions. The assessments for each actor, at each stage of product development, were discussed among the researchers, and the assessments were reviewed by interviewees and experts in the field, to provide feedback and some consensus on the levels of contributions.

Limitations of the Study

This study is subject to a number of limitations, which should be considered in any use of the findings, especially regarding the robustness of the conclusions. Four limitations are briefly discussed here.

First, the study was carried out with limited time, limited resources, and limited access to documents and individuals. The study was not designed or intended to be a full historical review of the archival record; and, indeed, the archives of some key institutions had been destroyed or were not openly available to the researchers. The study was designed as a background document for the Third External Review Committee of TDR, and each case study, therefore, was circumscribed in its scope, its data, and its style of presentation. The study is more of a focused evaluation than a full scholarly research project.

Second, the study examined institutional questions rather than scientific issues, and was carried out by researchers with political and organizational expertise rather than biological or parasitological expertise. The study addressed issues of institutional performance, and was not designed as a scientific review. The draft reports for each study were reviewed by individuals who were interviewed, in an effort to avoid scientific errors and factual mistakes. A number of interviewees provided several pages of comments on a draft. Their assistance is duly acknowledged and appreciated.

Third, this case represents a successful instance of product development by TDR, and therefore cannot be interpreted as representing the full universe of TDR activities for product development.

Fourth, the methods used to assess institutional performance and contribution are not well developed or universally accepted. This study sought to provide, from a position of independent observation, a narrative account of what happened at each stage of product development, and a description of the actions taken by TDR. The study sought to validate these observations by including differing perspectives on the same event, when possible. In addition, the narrative was reviewed by interviewees, to assure as much accuracy as possible. The semi-quantitative assessments of level of contribution for each actor, similarly, were reviewed by interviewees, and were revised when disagreement occurred and when a persuasive argument for revision was presented. Necessarily, these assessment and the revisions required some judgment by the researchers, based on the quality of evidence and the strength of arguments presented.

The assessment of contribution, thus, was complicated by a number of factors, from the perspective of methods. This case involves events that happened years ago and involved many players. The historical nature of the events and the cloudy nature of human memory sometimes made it difficult to ascertain exactly what happened at a particular meeting in the late 1970s, for example. The case depended on multiple players, with different interests and different organizational perspectives. These organizational pressures probably colored the recall of individuals and the representations of the past by institutions. Sometimes, different parts of the same organization had different views about what had happened and why. Finally, the success resulted from multiple factors and multiple organizations. The nature of success complicates efforts to attribute causal contributions, and especially to attribute relative weightings of contributions, because all the involved organizations seek to claim responsibility. (For failures, similar complications arise, but the claims of attribution usually seek to assign blame to other players.) For this study, the researchers sought to parse the multiple claims for success with as much independence and good judgment as could be mustered. But inaccuracies in fact and controversy over interpretation no doubt remain, for which the researchers accept responsibility.