Antiphytoviral Drugs Against Tomato Spotted Wilt Virus[1]

G. de Fazio[*], *M. Vicente*[**]

ABSTRACT

Many experiments have been carried out in the Plant Virology Section of the Biological Institute of São Paulo to discover an antiviral compound to control tomato spotted wilt virus (TSWV) in tobacco and tomato plants. The following compounds have been tested to date: acyclovir (9-[hydroxyethoxymethyl] guanine); amantadine (1-adamantanamine hydrochloride); aspirin (acetylsalicylic acid); bromopyrazino-pyrazine derivative (2,3-dihydroxy-6-bromopyrazino [2,3-B] pyrazine); carbendazim (methylbenzimidazole-2-yl-carbamate); dihydroxypropyl adenine ([R,S]-9-(2,3-dihydroxypropyl adenine); distamycin A (distamycin A hydrochloride); interferon (human amniotic interferon-Beta like); lauricidin (monogliceride of lauric acid); polyacrylic acid; ribavirin (1-beta-D-ribofuranosyl-1,2,4-triazole-3-carboxamide); tiazofurin (2-beta-D-ribofuranosyl-thiazole-4-carboxamide). Tiazofurin at the concentration of 100 mg/l was the most efficient drug to control TSWV in tomato plants when the leaves were sprayed twice, five days and 30 minutes after inoculation. Ribavirin also showed a remarkable inhibitory effect in tobacco ant tomato plants when the leaves were sprayed with 250 mg/l and 500 mg/l four and eight days before inoculation, respectively. Symptoms could also be suppressed when the solutions were sprayed 30 min after inoculation. Other substances which showed some inhibitory effect were: Acetyl-salicylic acid at 500 mg/l, sprayed 72 h before inoculation, and the bromo-pyrazino-pyrazine derivative at 400 mg/l brushed onto the leaves 24 h before virus inoculation.

COMPENDIO

Muchos experimentos han sido conducidos en la Sección de Virología de Plantas del Instituto Biológico de São Paulo, Brasil, con el intento de descubrir y seleccionar un compuesto antiviral para controlar el TSWV en plantas de tabaco y tomate. Los siguientes componentes fueron probados hasta el momento: acyclovir, amantadina, aspirina, bromopyrazinopyrazina, carbendazima, dihidroxipropiladenina, distamicina A, interferón humano, lauricidina, ácido poliacrílico, ribavirina y tiazofurina. Tiazofurina en una concentración de 100 mg/l fue la droga más eficiente para controlar TSWV en plantas de tomate, cuando sus hojas fueron pulverizadas dos veces durante treinta minutos, cinco días después de la inoculación. Ribavirina también mostró un efecto inhibitorio en plantas de tabaco y tomate cuando fueron pulverizadas con 250 mg/l y 500 mg/l, cuatro y ocho días antes de la inoculación, respectivamente. Los síntomas fueron totalmente reprimidos cuando las soluciones fueron pulverizadas treinta minutos después de la inoculación. Otras substancias que demostraron algún efecto inibidor fueron: ácido acetilsalicílico a 500 mg/l, pulverizado 72 h antes de la inoculación y el derivado bromopyrazinopyrazina pincelado sobre las hojas, 24 h antes de la inoculación con virus.

INTRODUCTION

Tomato spotted wilt virus (TSWV) has a world-wide distribution and one of the widest host ranges among plant viruses (4). The most important agricultural plants effected by TSWV are tomato, tobacco, pepper, potato and peanut (14). This virus presents some unique properties which include enveloped, roughly spherical particles, about 85 nm in diameter and is the only plant virus transmitted by thrips (14). Although TSWV is very unstable in plant

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* Current address: Biologist/Research Worker, Instituto Biológico, Seção de Virologia Vegetal, Caixa Postal 7119, 01051, São Paulo, Brasil.

** Fellow of CNPq, Ph.D.

extracts it can be easily transmitted by sap inoculation. TSWV is an ssRNA virus, probably positive sense (31).

In Brazil, some strains have become adapted to Solanaceous hosts, presenting a limiting factor for tomato crops under especial environmental conditions. Control measures involving attempts to introduce resistance in productive commercial tomato cultivars have failed, and the use of insecticides to control the vector, although reducing its incidence, has not adequately controlled the disease (5).

Many experiments have been carried out at the Plant Virology Section of the São Paulo Biological Institute to identify an antiviral compound which would control TSWV replication during the early phases of plant development, when the infection may become extremely severe. Different antiviral chemotherapic drugs were tested using tomato and tobacco plants as TSWV hosts.

The similarity between TSWV morphology and maturation processes with some animal viruses (Bunyaviridae) (24) suggested starting the screening tests with compounds which showed promising results against some animal viruses blocking specific virus enzymes. Thus, starting with ribavirin in 1977, the following compounds were tested: acyclovir, amantadine, bromo-pyrazino-pyrazine, dihidroxy-propyl adenine, distamycin A, interferon, lauricidin and tiazofurin, a drug structurally related to ribavirin. Since aspirin and polyacrylic acid may induce a systemic acquired resistance to viral infection, associated with the production of "b proteins" (18, 23, 26), they were included in the experiments. Furthermore, as systemic-acquired resistance may be due to a change in the endogenous hormonal balance, the systemic fungicide carben-dazim was also tested for its well known cytokinin activity (15).

MATERIALS AND METHODS

Virus source and inoculation

Plants were mechanically inoculated with a sap prepared using TSWV infected tomato leaves macerated in phosphate buffer 0.01 M containing 0.5% sodium sulphite + 0.1 M ascorbic acid in the proportion of 1 g fresh tissue/5 ml buffer. The leaves were dusted with carborundum before inoculation. Due to the instability of the virus all manipulations were carried out under cold conditions (± 4°C). To confirm the inoculum infectivity, all controls were inoculated after the treatments.

Compounds

The generic and chemical names of the compounds used as well as sources are listed in Table 1. Structural formulae of some are presented in Fig. 1.

Table 1. Compounds tested against tomato spotted wilf virns in tomato and tobacco plants.

Generic name	Chemical name	Source
Acyclovir	9-(hydroxyethoxy methyl guanine	(Dr H.J Schaeff) Borroughs Wellcome North Carolina (USA)
Amantadine (Symmetrel)	1-adamantanamine hydrochloride	Ciba-Geigy Wehr/Baden Germany
Aspirin	acetyl-salicylic acid	Bayer Laboratories, Brazil
Bromo-pyrazinopirazine derivative	2,3-dihydroxy-6-bromopyrazino (2,3 beta) pyrazine	Dr. A. Verini Carlo Erba Nerviano, Italy
Carbendazim (DPX-965-75)	methyl-benzimidazole-2-yl-carbamate	Dr Carlos Viana Du Pont, Brazil
Dihydroxy propyl adenine (DHPA)	(R,S)-9-(2,3-dihydroxypropyl) adenine	Dr. E De Clercq Rega Institute, Leuven, Belgium

Continuation Table 1.

Generic name	Chemical name	Source
Distamycin A	Distamycin A hydrochloride	Dr. A. Verini, Carlo Erba Nerviano – Italy
Interferon (Beta like)	Human amniotic interferon	Dr. R.R. Golgher Virus laboratory, Federal University of Minas Gerais – Belo Horizonte-Brazil
Lauricidin	Monoglyceride of lauric acid	(Dr. J. Kabara) Michigan State University, Michigan – USA
Polyacrylic acid (Versicol)	Polyacrylic acid M.W. 3 500	Allied Colloids Ltd. Bradford – England
Ribavirin (Virazole)	1-beta-D-ribofuranosyl-1,2,4,-triazole-3-carboxamide	Dr. I. Martirani ICN-Usafarma, São Paulo – Brazil
Tiazofurin	2-beta-D-ribofuranosyl-thiazole-4-carboxamide	Dr. R.K. Robins Cancer Res. Center-Brigham Young University – Provo – USA

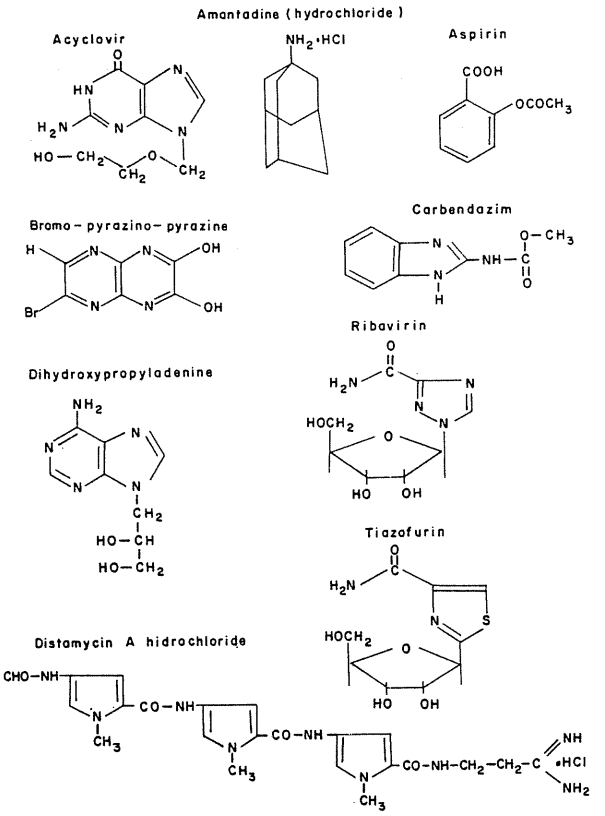

Fig. 1. Structural formulae of some antiviral compounds tested against tomato spotted wilt virus (TSWV).

Plants

The antiviral compounds were applied to tobacco 'White Burley' and/or tomato 'Sta. Cruz' plants. In all cases 10 potted, two to three- month old plants were used for each drug concentration, and for controls.

In order to verify if symptomless treated plants were virus-free, a recovery test was carried out when controls showed typical systemic symptoms (± 10 days after inoculation). For these recovery tests local reaction hosts such as *Phaseolus vulgaris* 'Manteiga' and *Petunia hybrida* were used.

The antiviral solutions were prepared with distilled water adding one drop of Tween 20/100 ml solution as a wetting agent. The solutions were mainly sprayed on the leaves once or more, according to the drug used (Tables 2 and 3). The plants were sprayed until dripping. Only one spray was applied for the majority of the chemicals before or after inoculation. For aspirin, three sprays were also applied at 24 h intervals and two sprays of dihydroxy-propyladenine were applied, immediately before and after inoculation. Brushing was the method used when the compounds were available in very small amounts.

This method consisted in applying the liquid on the leaf surface with the help of a soft brush. Irrigations were used only in the case of carbendazim; suspensions being prepared in water and applied twice to the soil of the potted plants with a 24 h interval.

Plants were kept in a glasshouse and observed daily during a period of 30 days. Local lesions appeared within approximately seven days in both host plants, tobacco and tomato. In tomato, visible local lesions could not be counted due to the coalescence of their borders. In tobacco local lesions were counted allowing evaluation of the inhibition percentage (IP) in which controls are compared to treatments according to the formula:

$$IP = (1\text{-}A/B)).\ 100,$$

where A= average number of local lesions in treated plants, and B = average number of local lesions in control plants.

Systemic symptoms could be observed in tobacco and tomato approximately 10 days after inoculation. The evaluation of the antiviral effect of each chemical was measured through the percentage of systemically infected plants (SIP) 20 d after inoculation.

Table 2. Effect of antiviral compounds against TSWV in tobacco plants.

Generic name	Method of application	Dosage[1]	IP[2]	SIP[3] (%)
Acyclovir	Sprayed once 30 min after inoculation	400 mg/l	0	100
		0	–	100
Amantadine (Symmetrel)	Sprayed once 30 min after inoculation	10 mg/l	37	100
		50 mg/l	24	90
		100 mg/l	33	100
		500 mg/l	43	100
		0	–	100
Aspirin	Sprayed once 24, 48 or 72 h before inoculation	250 mg/l	24 h 8	83
			48 h 52	67
			72 h 54	67
		500 mg/l	24 h 6	67
			48 h 84	17
			72 h 90	17
		0	–	90
	Sprayed 3 times with 24 h interval before inoculation	250 mg/l	52	50
		500 mg/l	84	30
		1 000 mg/l	94	10 (phytotoxic)
		0	–	100
Bromo-pyrazino-pyrazine derivative	Brushed once, 2 h before inoculation	200 mg/l	100	40
		400 mg/l	100	10
		0	–	80
Carbendazim (DPX-965-75)	Irrigated twice, 24 and 48 h before inoculation	0 5 g/l	0	100
		1 0 g/l	0	100
		2 0 g/l	8	85
		5 0 g/l	35	82
		10 0 g/l	57	100
		0	–	90
Dihydroxy propyl adenine (DHPA)	Sprayed twice, 5 min before and 5 min after inoculation	500 mg/l	26	50
		0	–	70
Distamycin A	Brushed once, 2 h before inoculation	200 mg/l	0	80
		400 mg/l	49	40
		0	–	80

Continuation Table 2.

Generic name	Method of application	Dosage[1]	IP[2]	SIP[3] (%)
Interferon (beta-like)	Brushed once, 72 h before inoculation	0.001 U/ml	60	85
		1 U/ml	43	90
		100 U/ml	50	90
		0	–	90
Lauricidin	Sprayed once, 30 min after inoculation	1 ml/l	0	100 (phytotoxic)
		0		100
Polyacrylic acid (Versicol)	Sprayed once, 30 min, 24 h, 48 h, 72 h or 96 h before inoculation	200 mg/ml	30 min 0	100
			24 h 61	100
			48 h 83	100
			72 h 57	100
			96 h 45	100
		0	–	100
	Sprayed once, 30 min or 48 h before inoculation	10 mg/ml	30 min 0	100
			48 h 86	90
		20 mg/ml	30 min 0	100
			48 h 89	70
		40 mg/ml	30 min 0	100
			48 h 87	100
		0	–	100
Ribavirin (Virazole)	Sprayed once, 96 h before inoculation	100 mg/l	60	60
		250 mg/l	60	0
		500 mg/l	60	0
		0	–	100
	Sprayed once, 30 min after inoculation	100 mg/l	0	10
		250 mg/l	0	0
		500 mg/l	0	0
		0	–	100
Tiazofurin	Sprayed once, 30 min after inoculation	100 mg/l	93	20
		200 mg/l	100	0 (phytotoxic)
		0	–	100

1 0 = control
2 Inhibition percentage in relation to the number of local lesions calculated seven days after inoculation.
3 Systemically-infected plants 20 days after inoculation.

Experiments were repeated twice and data expressed in Tables 2 and 3 contain the results of one of the tests.

RESULTS

The results obtained with the antiviral compounds tested against TSWV in tobacco and tomato plants are presented in Tables 2 and 3.

Acyclovir: Acyclovir is a derivative of guanine which selectively inhibits the replication of herpes simplex virus types 1 and 2. It is converted to triphosphate in herpes-infected cells being, in this form, a more potent inhibitor of virus specific DNA polymerase than of the cell alpha-DNA polymerase (1, 16).

This drug showed no inhibitory effect against TSWV, even at the high concentration of 400 mg/l, when sprayed on tobacco plants 30 min after inoculation.

Amantadine: Amantadine has been show to be effective in the prevention and treatment of an (SS)

Table 3. Effect of antiviral compounds against TSWV in tomato plants.

Generic name	Method of application	Dosage[1]	SIP[2]
Aspirin	Sprayed once. 72 h before inoculation	250 mg/l	100
		500 mg/l	75
		0	100
Dihydroxy propyl adenine (DHPA)	Sprayed once, 30 min before inoculation	800 mg/l	100
		0	100
Lauricidin	Sprayed once, 30 min after inoculation	1 ml/l	100 (phytotoxic)
		0	100
Polyacrylic acid (Versicol)	Sprayed once. 48 h before inoculation	20 mg/ml	100
		40 mg/ml	100
		0	100
Ribavirin (Virazole)	Sprayed once, 30 min after inoculation	100 mg/l	60
		200 mg/l	80
		300 mg/l	60
		400 mg/l	70
		500 mg/l	10
		0	90
	Sprayed twice, 30 min and 24 h after inoculation	500 mg/l	45
		0	100
Tiazofurin	Sprayed once. 30 min after inoculation	50 mg/l	80
		150 mg/l	40
		200 mg/l	40
		0	100
	Sprayed once, 5 or 9 d before inoculation	100 mg/l	5 days 100 9 days 100
		0	100
	Sprayed once, 5 or 9 d after inoculation	100 mg/l	5 days 20 9 days 100
		0	100
	Sprayed twice, 30 min and 5 d after inoculation	100 mg/l	10
		0	100

1 0 = Control

2 Systemically infected (%) plants 20 days after inoculation

RNA human virus, influenza type A, but not types B or C (17).

In tobacco it inhibited local lesions induced by TSWV in low percentage (below 45 per cent). Moreover the drug did not protect the plant against the spread of the systemic infection.

Aspirin: Acetylsalicylic acid and salicylates may induce new proteins in plants which are characteristic of a hypersensitive reaction to pathogens (23, 26, 34). When aspirin was applied once before virus inoculation in tobacco plants, the highest inhibitory effect was observed when 500 mg/l was sprayed 48 or 72 h before TSWV inoculation (SIP 17 per cent) (11). Aspirin applied three times before virus inoculation in concentrations of 250, 500 and 1000 mg/l, inhibited local lesions inducing IPs of 52 %, 84 % and 94 % respectively. At 1000 mg/l however, the drug induced a strong phytotoxic effect consisting of leaf blade burning, although the solutions were always neutralized to pH 7 with sodium bicarbonate 1.0 M. In tomato plants under similar conditions a low protective effect could be observed when 500 mg/l

was sprayed 72 h before virus inoculation (SIP 75 per cent) (11).

Bromo-pyrazino-pyrazine: The compound showed *in vitro* antiviral activity against RNA and DNA animal viruses (30).

In tobacco plants the drug was applied 2 h before virus inoculation at concentrations of 200 and 400 mg/l. The compound was effective only at the 400 mg/l concentration, delaying the appearance of systemic symptoms (9). This drug was not tested in tomato plants.

Carbendazim: Carbendazim, a well known systemic fungicide used in agriculture, indirectly inhibits viral RNA synthesis by maintaining the host in a state unsuitable for viral multiplication (15).

When tobacco plants were irrigated twice with an aqueous suspension of the compound (24 h and 48 h before virus inoculation) a bimodal effect against TSWV was observed: low dosages such as 0.5 g/l and 1.0 g/l increased the number of local lesions with the IP zero. High dosages such as 10.0 g/l reduced the number of local lesions to 57 inhibition percentage. However, in all concentrations the drug was unable to control the spread of the systemic infection allowing the appearance of a high percentage of systemically-infected plants 20 d after inoculation (10).

Dihydroxypropyl adenine: (R,S)DHPA is a S-adenosylhomocysteine hydrolase (SAH-hydrolase) inhibitor with broad spectrum antiviral activity. It acts against some DNA viruses, most (-) and (±) RNA viruses but not (+) RNA viruses, except some plant viruses: Potex, Poty, Tobamo and Tymoviruses (6, 12, 13). Its effect was null against TSWV in tomato and very low in tobacco plants (12).

Distamycin A hydrochloride: Distamycin A, a synthetic antibiotic, inhibits the multiplication of some animal and human DNA viruses (3, 19). When used against TSWV in tobacco plants 2 h before virus inoculation, it inhibited local lesions, inducing almost 50 per cent IP at a 400 mg/l concentration. In this same concentration the systemic reaction in tobacco plants decreased 50 per cent in relation to controls (9).

Interferon: It was demonstrated that interferons may protect tobacco plants or protoplasts against TMV infection (25, 27). Similar results were obtained by Vicente *et al.* (32, 33) using human gamma and human amniotic interferons against different plant viruses.

Human amniotic interferon (Beta-like) when brushed on tobacco leaves 72 h before TSWV inoculation, induced inhibition percentages around 50 even at a low concentration, as low as 0.001 U/ml. However there was no protection in relation to the systemic infection.

Lauricidin: Lauricidin is a monolaurin compound and a monoglyceride of lauric acid, acting as a detergent. It is the trade name of a monolaurin, consisting of approximately 90 per cent 1-ester and 10 per cent 2-ester and has been effective against lipid-containing bacterial viruses and enveloped viruses (21). When sprayed at a concentration of 1 ml/l on tobacco and tomato plants after inoculation, it showed no inhibitory effect on tomato spotted wilt virus. A strong phytotoxicity in the form of burning of the leaf blades could be observed in both tobacco and tomato plants.

Polyacrylic acid: Polyacrylic acid was considered a chemical able to induce both interferon in animals and resistance in plants (18, 22). The drug was effective in controlling local lesions in tobacco plants with a time interval of 48 h between treatment and inoculation. Lower or higher time intervals were less effective. When the systemic infection was evaluated, no protection could be observed in any case. In tomato plants TSWV lesions could not be counted and the drug was completely ineffective in controlling systemic reaction, as observed in tobacco plants (11).

Ribavirin: Ribavirin, synthesized by Witkowski in 1972, was shown to have a extremely broad spectrum antiviral activity *in vitro* against animal viruses (28). The drug was tested against some plant viruses showing promising results (20).

In tobacco plants, pre-treatments with 250 mg/l applied 96 h before virus inoculation, were considered the best combination treatment to drastically reduce the number of systemically infected plants. The drug was also shown to be highly active when sprayed at 500 mg/l even eight days before inoculation (8). Treatments with 100 mg/l, 250 mg/l or 500 mg/l when applied 30 min after inoculation, were also

effective against TSWV systemic infection (7, 8). In this case, however, the drug did not inhibit local reaction but a smaller size of the local lesions in relation to the control was observed (8). In tomato plants, the most efficient concentration to control TSWV was 500 mg/l when applied 30 min after inoculation. Tobacco and tomato plants sprayed with ribavirin at 500 mg/l in the first two days, showed a chlorosis of the apical bud which was overcome after three days.

Tiazofurin: Tiazofurin was reported to be active as an anti-tumor compound and also as an anti-viral agent (29). In tobacco plants, 100 mg/l applied 30 min after inoculation was efficient in suppressing TSWV local and systemic infection, and 200 mg/l was highly phytotoxic to the plant. However, in tomato plants, this same concentration did not show any phytotoxicity and also reduced the percentage of systemically infected plants.

It was verified in tomato plants, that pre-treatments did not inhibit systemic reaction; and that the drug was highly efficient in controlling systemic infection, especially when applied once or twice after inoculation at 100 mg/l, and when the second spray was applied five days after inoculation. In all cases, a delay in the appearance of systemic symptoms was observed in treated tomato plants, indicating a decrease in virus spread and virus concentration within tomato plants (2).

Phytotoxicity: Among tested compounds some were highly phytotoxic to the plants in the dosages applied, inducing a burning of leaf blades or an irreversible wilting. To this group belonged aspirin at 1000 mg/l and lauricidin at 1 ml/l. Tiazofurin was phytotoxic to tobacco plants only at the 200 mg/l concentration. The phytotoxicity of ribavirin at 500 mg/l consisted of a strong chlorosis of the youngest leaves (apical buds) in tobacco and tomato plants, which disappeared in three days. In tobacco a narrowing of the leaf blades followed the symptoms.

DISCUSSION

Ribavirin and tiazofurin were the most efficient drugs to control TSWV in tobacco and tomato plants. Both are guanosine analogs with similar structural relationships.

Comparing the results obtained with these two compounds, low concentrations of tiazofurin were more efficient than similar ribavirin dosages in suppressing TSWV systemic infection in tomato plants (2). On the other hand ribavirin was already tested against at least 10 different plant viruses being effective not only in experimental tests but also in obtaining virus-free plants from infected stocks (20). Thus, the effect of tiazofurin, although not yet explored against other plant viruses, must be emphasized for its strong inhibitory activity, even when applied after inoculation (2).

According to Hansen (20) a broad spectrum antiviral chemical, produced at reasonable costs and ecologically neutral, will facilitate practical usage of antiviral chemicals in agriculture and horticulture.

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RESEÑA DE LIBROS

SPARKS, D.L.; SUÁREZ, D.L. (EDS.). 1991. Rates of soil chemical processes. Madison, Wisconsin, Estados Unidos, Soil Science Society of America. 302 p.

La investigación reciente ha mostrado que las tasas con que ocurren las reacciones en suelos son de gran importancia. Algunos trabajos relacionados con este tema se presentaron en un simposio de la reunión anual de la *Soil Science Society of America*, y muchas de estas contribuciones, en forma más elaborada, constituyen capítulos de este volumen. El material presentado y los métodos propuestos representan los conceptos más recientes y adelantados para analizar procesos químicos en suelos. El texto se preparó para especialistas y estudiantes graduados avanzados en química de suelos y campos afines como la geoquímica, química de sedimentos y química del medio ambiente, por lo que para su aprovechamiento se requieren sólidos conocimientos de química.

Este texto permitirá, si se poseen conocimientos sobre la cinética de las reacciones paralelas, comprender mejor lo que ocurre con las diferentes substancias en el suelo. Seis de los once capítulos del libro se dedican al estudio de la cinética de procesos químicos en suelos o de casos particulares, tales como la cinética de las reacciones redox de los óxidos de manganeso en suelos, la de la absorción de substancias orgánicas en suelos y la de la absorción de iones sobre substancias luínicas.

Debido a que la adquisición de información nueva requiere técnicas novedosas y una interpretación adecuada, se incluye un capítulo sobre cómo obtener y analizar datos en cinética de suelos y cómo preparar modelos con esta información.

Como es costumbre en libros de este nivel, todos los capítulos tienen una amplia bibliografía, especialmente sobre procesos ambientales cuidadosamente estudiados en Europa.

ELEMER BORNEMISZA
UNIVERSIDAD DE COSTA RICA