SOME ASPECTS OF THE CHEMISTRY AND BIOLOGY
OF THE GENUS HYPOCREA AND ITS ANAMORPHS,
TRICHODERMA AND GLIOCLADIUM

A. TAYLOR
National Research Council of Canada
Atlantic Research Laboratory
Halifax, N.S. B3H 3Z1

The literature describing the occurrence, some aspects of the physiology and toxicology of the metabolic products of *Hypocrea, Gliocladium* and *Trichoderma* spp. is reviewed. A list of known metabolites of this group of fungi has been assembled and the common physical properties of these compounds are given when they have been reported. Such data as have been published on the toxicity of these metabolites is summarised, with particular emphasis on suitable review articles. An attempt is made to provide a comprehensive list of agents, known as potential inhibitors of the growth of these fungi.

La littérature décrivant quelques aspects de la physiologie et de la toxicologie des métabolites d'*Hypocrea, Gliocladium* et *Trichoderma* spp. est passée en revue. Une liste des metabolites connus de ce groupe de moisissures est dressée et les propriétés physiques courantes sont données si connues. Les informations publiées concernant la toxicité de ces mètabolites sont resumées avec reference aux articles de revue appropriées. L'auteur tente de donner une liste compréhensive des agents potentiellement inhibiteurs de la croissance de ces moisissures.

Introduction

The taxonomy of the three genera, *Hypocrea, Gliocladium,* and *Trichoderma* is in some respects confused. Authoritative studies of these taxonomic problems may be found in Gams (1971), Webster and Lomas (1964) and Rifai (1969), but there are many examples in the literature that report difficult classification problems (e.g. Brian 1944, Brewer and Taylor 1981). For the purpose of this review, therefore, the position is taken that the three genera are very closely related and that serious lacunae would appear should one or other be excluded. There is also some debate concerning the classification of the fungus that produces cyclosporins; it was originally thought to be *Trichoderma polysporum* but later work has used the name *Tolypocladium inflatum* (Gams 1971b). For the purpose of the review it is assumed that the taxonomy remains uncertain.

The first part of the review is devoted to the substrates on which the organisms are found, with emphasis on the more unusual of these; the second part attempts to give a comprehensive account of the very wide variety of known metabolites and the third part describes what is known of their toxicities. These fungi are heavily involved in the natural degradation of organic substrates and hence a very large body of work has been done in attempts to protect e.g. wood from their activities. The fourth part of the review is therefore devoted to a description of the agents that have been used to this end and to their effectiveness.

The literature has been thoroughly searched up to and including December 1984, but additional references from 1985 will be found where these have come to my attention during that year. I have not read all the papers cited in this review; articles that I have not read can be distinguished by a reference to Chemical Abstracts.

Natural and unusual habitats of fungi of the genera Hypocrea, Gliocladium and Trichoderma

Hypocrea spp. are usually found on decaying wood but it has been known for more than 100 years that frequently they are parasites on other fungi (see e.g. Saccardo 1883, Tabata and Kondo 1977). By contrast the genera *Gliocladium* and *Trichoderma* are found very frequently in the soils of the planet. There have been a number of extensive studies of the soil ecology of these organisms. For example, Berestetskii, Patyka and Nadkernichuyi (1977) studied more than 700 isolates of *Trichoderma* from soils and Brewer and Taylor (1980) found that *Gliocladium roseum*, *Trichoderma koningii* and *Trichoderma hamatum* accounted for about 6% of some 25,000 fungal isolates collected over a 10 year period from pasture soil at Nappan, Nova Scotia. Many of the species of the three genera are capable of the hydrolysis of plant polysaccharides, especially cellulose, and a very large number of studies of this process both at the cellular and enzymic levels has been recorded in the literature. The impetus behind this work is the conversion of plant waste e.g. coffee grounds (Aguirre *et al.* 1976) into digestible components e.g. fructose in the diet of humans and domestic animals. This topic has been reviewed on many occasions and is not repeated here; the interested reader should consult for example Ryu and Mandels (1980).

The substrates on which these fungi have been observed to grow are given in Table I. It is clear from the data in the Table that these organisms can grow on a diverse range of substrates from stainless steel (Brown and Pabst 1977), presumably with a carbon content to bitumen used for road construction (Khimerik and Koval 1977). However a ubiquitous substrate for most of these fungi is wood and the various products manufactured from it (Merrill *et al.* 1965). Viable *Trichoderma* spp. have been found in thin cross-sections of timber (Dinulescu 1979) and this is perhaps not surprising because of the growing appreciation of the importance of endophytic fungi in higher plants (Claydon *et al.* 1985). The economic losses resulting from fungal degradation of timber and associated products has led to considerable effort to control their growth on this substrate. This aspect is discussed in greater detail in a later part of the review, but it is relevant to mention at this point that alkali treatment of wood chips before storage (Bergman and Nilsson 1971) was not particularly effective and that fumigation with formaldehyde resulted in the discovery that this agent (and other C_1 compounds) were utilised by *Gliocladium deliquescens* with alacrity (Sakaguchi *et al.* 1976). It is known (Moelhave 1977) that the formaldehyde concentration in aggregated wood products cemented with urea-formaldehyde resins is proportional to the humidity; that *Trichoderma* spp. grown on such resins (von Kerner-gang and Hoffmann 1982) and hence it may be concluded that these fungi are natural components of all materials containing products derived from wood. Laboratory studies (Gauze *et al.* 1983, Brewer *et al.* 1982, Sierota 1977) have shown that these fungi grow well on very simple media containing only one of a wide range of carbohydrate sources, and simple nitrogen containing compounds e.g. urea (Nelson 1972, 1976). It follows that these organisms will grow rapidly on almost any natural substrate providing that both the temperature and humidity conditions are suitable. Little is known of the range of humidities conducive to growth (but see Widden and Abitol 1980); much more is known about the temperature range (Brewer and Taylor 1980) which is relatively wide (5-35°).

Metabolites of fungi of the genera Hypocrea, Gliocladium and Trichoderma

For the purpose of this review, the metabolic products of these fungi are separated into groups; the grouping is based on the chemistry of the metabolites and particularly on their probable mode of biosynthesis. The appearance of a compound (or a mixture of very closely related compounds) in one of the Tables implies that there

Table I Substrates supporting growth of *Hypocrea* spp. *Gliocladium* spp. or *Trichoderma* spp.

Organism	Substrate	Reference
Hypocrea nigricans	Lentinus edodes	Tabata & Kondo (1977)
	Cellulose	Doi et al., (1972)
Hypocrea peltata	Cellulose	Doi et al., (1972)
Hypocrea schweinitzii	Lentinus edodes	Tabata & Kondo (1977)
Gliocladium sp.	Groundnut	Madaan & Chohan (1978)
	Epichlorhydrin cross-linked cellulose	Dao Cong Dan et al., (1980)
Gliocladium varians	Rhizospheres of barley & oats	Sukhorukova (1972)
Trichoderma spp.	Barley β-glucan	Igaue (1966)
	Cork	Cook & Harrington (1948)
	Lentinus edodes	Tabata & Kondo (1977)
	Rhizoctonia spp.	Allen & Haenseler (1935)
	Phythium spp.	Haenseler & Allen (1934)
	Petroleum waxes	Bilai et al., (1965)
	Motor oil recovered from Chesapeake Bay	Colwell et al., (1974)
	Road building bitumen	Khimerik and Koval (1977)
	Polyvinyl chloride/dibutyl sebaccite/dioctyl phthalate	Berk (1951)
	Polyvinyl chloride	Yamano (1979)
	Polyvinyl alcohol based polymer	Shteinberg et al., (1983)
	Acetylated cellulose	Abramova et al., (1973)
	Ethylene/vinyl acetate copolymers	Griffin and Mivetchi (1977)
	Paint	Kleus and Lang (1956)
	Organosilicon protective coatings	Pashenko et al., (1978)
	Chromed leather (N. American)	Mitzutani et al., (1980)
	Wood shavings impregnated with urea	Nelson (1972)
	Silicate rocks and soil	Henderson and Duff (1963)
	Stainless steel and aluminum alloys	Brown & Pabst (1977)
	Domestic humidifiers	Burge et al., (1980)
Trichoderma hamatum	Diesel fuel	Suess & Netzsch-Lehner (1969)
Trichoderma harzianum	Lentinus edodes	Tabata & Kondo (1977)
	Ferric hydroxide mud impregnated with oil	Gudin and Chater (1977)
Trichoderma koningii	Wood pulp	Wakazawa et al., (1965)
Trichoderma lignorum	Rhizoctonia solani	Weindling (1932)
		Daines (1937)
	Phytophthora parasitica	Weindling (1932)
Trichoderma lignorum	Sclerotium rolfsii	Weindling (1932)
	Pythium sp.	Weindling (1932)
	Rhizopus spp.	Weindling (1932)
	Actinomyces scabies	Daines (1937)
	Wood resin	Nilsson and Assarsson (1970)
	Diglycidyl-hydroquinone ether polymers	Anisimov et al., (1977)
Trichoderma viride	Wood	Stranks (1971)
	Wood	Verrall (1949)
	Chitin	Kawasaki and Ito (1966)
	Rye-grass straw	Han and Anderson (1975)
	Synthetic rubbers and polyethylene	Mazur (1979)
	Vanillin	Moreau and Augier (1962)
	Allyl alcohol	Jackson (1973)

exists in the literature, data from the measurement of physical properties that allow competent chemists to judge if natural products they isolate are identical or not. A few other materials that have been reported in Abstracts in papers I have been unable to read are reported in the text. In addition, such simple volatile metabolites - ethyl alcohol, ethyl acetate, sec-butyl alcohol, isoamyl alcohol, octanol, octa-3-one, oct-1-ene-3-ol (Saito et al. 1981) and acetaldehyde (Dennis and Webster 1971) have not been included in the Tables. The biological significance of the production of volatile metabolites by these fungi have interested mycologists for many years (Bilai 1956, Hutchinson and Cowan 1972, Tamimi and Hutchinson 1975). This has been particularly the case because of the part that may be played by such metabolites in the sexual reproductive cycle of many Phytophthora spp. (Reeves and Jackson 1972, Pratt et al. 1972); species responsible for diseases in some of the world's most important agricultural crops. However a systematic examination of a large number of isolates for volatile metabolites has not been recorded. Reference to the melting points given in the Tables shows that many metabolites have melting points below 150° - all such compounds can be considered to have measurable vapour pressures.

Polyketide metabolites produced by Hypocrea, Gliocladium and Trichoderma
A list of these compounds is given in Table II. Apart from the bis-anthraquinone (XXXIII) most of these compounds were studied in the era 1950-1965 i.e. before the advent of high pressure liquid chromatography. It is likely that there are many more variations in the resorchinol (Pettersson 1965) and hydroquinone (Brian et al. 1951, Vischer 1953) components than those recorded in the Table. The benzoquinones,
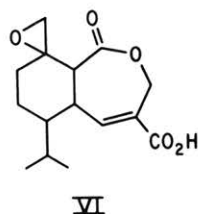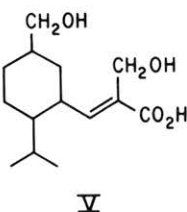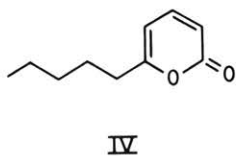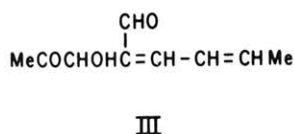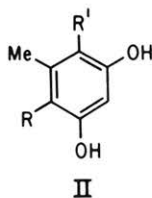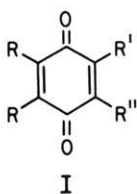
and anthraquinones are easily reduced to the leuco forms and strong evidence has been presented (Pettersson 1965) that these are the true natural products - the more volatile quinones being artefacts of the isolation procedure. Such compounds are, of course, vat-dye stuffs, or in other words they form stable complexes with natural carbohydrate polymers. Most of these compounds are biosynthesised, often in high yield, from acetate by a polyketide route and are formed after the end of the so-called logarithmic phase of growth, usually when all source of nitrogen has been exhausted (Pettersson 1965, Gatenbeck 1958). The diphenyl ether metabolites (XXXI) isolated
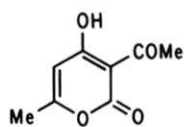
Table II Polyketide metabolites of Hypocrea spp., Gliocladium spp. and Trichoderma spp.

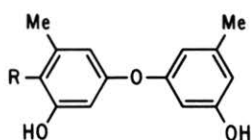| Trivial name	Structure	m.p.	Producing organism	References
Tartronic acid	$HOCH(CO_2H)_2$	158-60°	T. pseudokoningii	Kamal et al., (1971)
Aurantiogliocladin	I, R=Me, R'=R''=OMe	63°	G. roseum	Brian et al., (1951)
Gliorosein	Dihydro I, R=Me, R'=R''=OMe	48°		
	I, R=Me, R'=R''=OH	182°		Pettersson (1964)
	I, R=Me, R'=OH, R''=OMe	70°		
	I, R=OMe, R'=R''=H		T. pseudokoningii	Kamal et al., (1971)
Orcinol	II, R=R'=H	108°	G. roseum	Pettersson (1965)
	II, R=Me, R'=H	136°		
	II, R=Me, R'=CO_2H	158°		
Dehydroacetic acid	XXX	109-11°	H. sulphurea	Nair and Carey (1979)
	XXXI, R=H		H. citrina	
	XXXI, R=CO_2H	194°		
Pachybasin	XXXII, R=R³=H, R¹=OH, R²=Me	176°	T. viride	Slater et al., (1967)
Chrysophanol	XXXII, R=R¹=OH, R²=Me,	194°		
	R³=H		H. austragrandis	Nago and Ishikawa (1970)
Emodin	XXXII, R=R¹=R³=OH, R²=Me	256-8°	T. viride	Slater et al., (1967)
			H. austragrandis	Nago and Ishikawa (1971)
Hypochrysophanol	unknown	205°		
SC2051	XXXIII		Trichoderma sp.	Manyu (1980)
	IV, x=CH=CH		T. viride	Moss et al., (1975)
	IV, x=Ch_2-CH_2			Collins and Halim (1972)
			Trichoderma sp.	Kikuchi et al., (1974)

Table III Terpenoid metabolites of Hypocrea spp., Gliocladium spp. and Trichoderma spp.

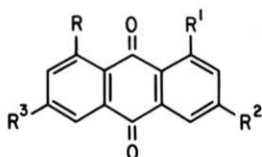| Trivial name	Structure	m.p.	$[\alpha]_D$	Producing organism	References
	3-Hydroxy-3,4-di methylpentanoic acid	100°/.05 mm	-1.1°	G. deliquescens	Hanson and O'Leary (1981)
(+)-R-avellaneol	III		+39°	H. avellania	Ananthasubramanian et al., (1978)
Gliocladic acid	V			G. virans	Itoh et al., (1982)
				T. viride	
Heptelidic acid = avocetin	VI	62-5°	+7.4°	G. virans	Itoh et al., (1980) Stipanovic and Howell (1983)
Cyclonerodiol	VII		-20°	T. polysporum	Fujita et al., (1984)
Cyclonerodioloxide	VIII	47-50°	-20°		
Trichodermin = WG 696	IX, R=R'''=H, R'=Me, R''=OAc	46°	-11°	T. viride	Godtfredson and Vangedal (1965)
				T. polysporum T. sporulosum	Adams and Hanson (1972)
				H. austrograndis	Nago and Ishikawa (1971)
Trichodermol = roridin C	IX, R=R'''=H, R'=Me, R''=OH	115°	-33°	T. polysporum T. sporulosum	Adams and Hanson (1972)
T₂ toxin	IX, R=OCOCH₂CHMe₂, R'''=OH, R'=CH₂OAc, R''=OAc	151-2°	+15°	T. lignorum	Bamburg and Strong (1969)
HT₂ toxin (?)	IX, R=OCOCH₂CHMe₂, R'=CH₂OAc, R''=R'''=OH				
Trichodermene A	XX			T. pseudokoningii	Kamal et al., (1971)
Viridin	X, Y=O	245°	-224°	T. viride	Brian et al., (1946) Grove et al., (1965, 1966)
Viridiol	X, Y=H, OH	198-201°			Moffatt et al., (1969)
Pyrocalciferol	XXVI	93-5°	+502°	T. pseudokoningii	Kamal et al., (1971)

from *Hypocrea citrina* (Nair and Carey 1979) are derived from orcinol (II, R=R'=H, Yamamoto *et al.* 1972) and the acid (XXXI, R=CO_2H) has also been isolated from *Aspergillus fumigatus.*
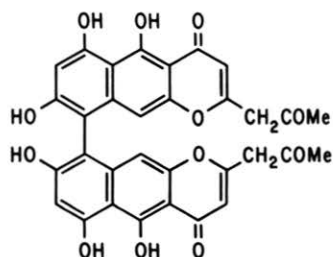
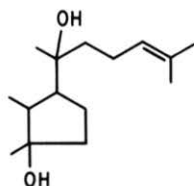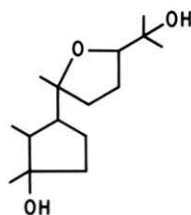$$\underline{\textbf{XXX}} \qquad \underline{\textbf{XXXI}} \qquad \underline{\textbf{XXXII}}$$

$$\underline{\textbf{XXXIII}}$$
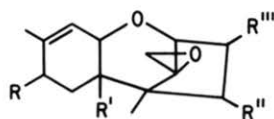
$$\underline{\textbf{VII}} \qquad \underline{\textbf{VIII}} \qquad \underline{\textbf{IX}}$$
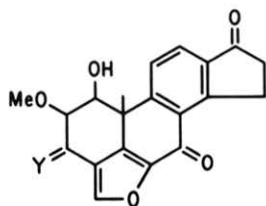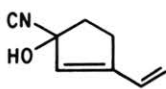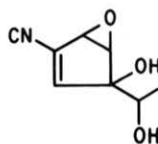
$$\underline{\textbf{X}} \qquad \underline{\textbf{XI}} \qquad \underline{\textbf{XII}}$$

Oligomers of mevalonic acid produced by Gliocladium spp., Hypocrea spp., and Trichoderma spp.

A list of these compounds is given in Table III. Most of the compounds in the Table are low-melting solids. The structures of all, with perhaps the exceptions of avellaneol and trichodermene A have been rigorously established, though the absolute configuration of T_2-toxin and its congeners has not yet been determined. There have been extensive studies on the biosynthesis of trichodermin (IX, R=R'''=H, R'=Me, R''=OAc; Achilladelis et al. 1972) and heptelidic acid (VI, Stipanovic and Howell 1983). Both arise from farnesyl pyrophosphate, folded in the same way, but the carbonium ion generated by the leaving pyrophosphate group cyclises in the former case (Arigioni et al. 1973) as shown in XXVII and in the latter case as shown in XXVIII. In both cases
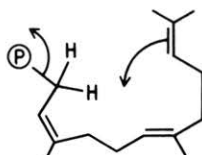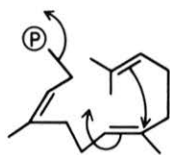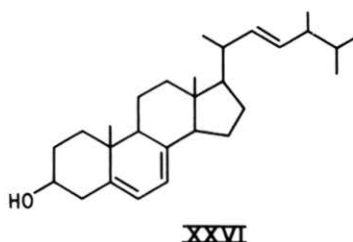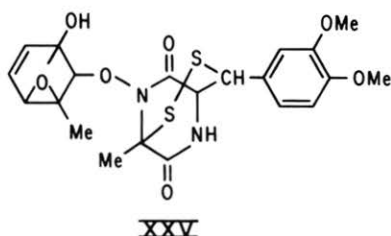

XXV

XXVI

XXVII

XXVIII

XXIX
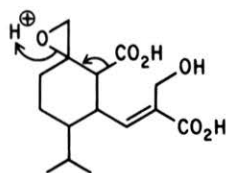
the following reaction is a hydride shift nominally over 4 carbon atoms in the trichothecin and 3 in the example of heptelidic acid. There is ample precedent for the subsequent rearrangements. It has been suggested (Itoh et al. 1982) that gliocladic acid (V) is biodegradatively derived from heptelidic acid by decarboxylation as shown in XXIX. Cyclonerodiol (VII) and its congeners are also known to be sesquiterpenoid (Pitel et al. 1971) cyclisation products of farnesyl pyrophosphate.

A number of C_{20} and higher oligomers of mevalonic acid are given in Table III of which viridin (X) and its derivatives are perhaps the most interesting. These compounds are not diterpenes but are biodegradation products of steroid intermediates (Blight et al. 1968) e.g. lanosterol (Golder and Watson 1980), and squalene (Hanson and Wadsworth 1979). Some work has been done on the biosynthesis of avellaneol (III, Nair et al. 1982) who have shown that $*CH_3CO_2^-$ and $CH_3*CO_2^-$ are recovered in about 2% yield in avellaneol but that $*CH_3*CO_2^-$ is not incorporated intact. It is therefore possible that the biosynthesis of this metabolite (III) is not terpenoid but is analogous to that of the isocyanides discussed in the next section.

*Metabolites derived from α-amino acids by degradation or elaboration*

A list of these compounds is given in Table IV. About eight cyclopentyl isocyanides

Table IV Non-polypeptide metabolites of Gliocladium spp. and Trichoderma spp. derived from α-amino acids.

Trivial name	Structure	m.p.	$[\alpha]_D$	Producing organism	References
Isonitrin D	XI	55°	+68.5°	T. harzianum	Fujiwara et al., (1982)
Isonitrin B	XII	89°	-89.9°	T. hamatum	
Isonitrin A	XIII	91°	+9°		
Trichoviridin = isonitrin C	XIV	102°	-41.2°	T. viride	Tamura et al., (1975) Nobuhara et al., (1976)
Dermadin	XV	120-5°	+133°	T. hamatum	Brewer et al., (1982)
	XVI				
	XVII				Baldwin et al., (1985)
	XVIII (CO_2Me)				
TP-1		185-7°		T. polysporum	Fujita et al., (1984)
Valinotricin	XIX	128-9°	-65.7°		
	3-Benzyl-6-hydroxy-methylenepiperazine-2,5-dione			G. virens	Behling and Fischer (1980)
Gliotoxin	XXI	221°	-255°	G. fimbriatum	Johnson et al., (1943)
				T. hamatum	Hussain et al., (1975)
				G. deliquescens	Hanson and O'Leary (1981)
	XXII, R=H	68-9°	-55.6°		
	XXII, R=$CH_2CH=CMe_2$		-26.8°		
	XXIII (?)				
	XXIV				Kirby et al., (1980)
Gliovirin	XXV	247-9°	-97°	G. virens	Stipanovic and Howell (1982)
	3,6-Dibenzylpiperazine-2,5-dione	303-8°	-167°		
Trichorin A	unknown	234-46°	-190°	Trichoderma sp.	Katayama et al., (1977)
Trichorin B		212-4°			

that have been fully characterised, are now known. Their structures are given in formulae XI to XVIII - the latter is only known as its methyl ester, which is not a natural product (Baldwin et al. 1985). There are, however, many more such compounds in fermentation broths of *T. hamatum, T. koningii, T. harzianum* and *T. polysporum* and it is likely that many of these will be characterised now that it is possible to obtain stable co-ordination complexes of them with rhodium pentamethylcyclopentadiene
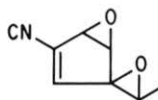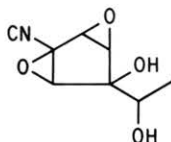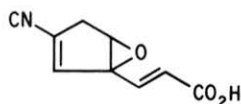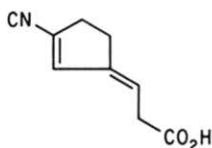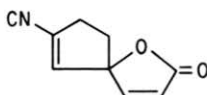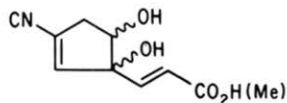
isothiocyanate (Hanson et al. 1985). The known compounds vary in instability from trichoviridin (XIV) - a stable crystalline solid to 3-(3'-isocyancyclopent-2-enylidene-) propionic acid (XVI), which has a half-life in dilute aqueous solution of pH 8 of about 4 h. All of these compounds are volatile and an early method of recovery was by steam
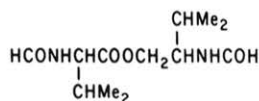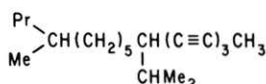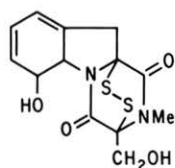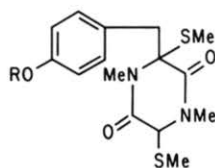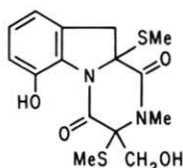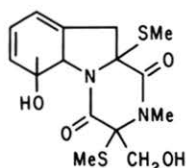
distillation at about 35°/1 mm. These isocyanides are biodegradation products of tyrosine (Baldwin et al. 1985, Parry and Hanh Phuoc Buu 1982) and are formed by oxidation of the aromatic ring at the phenolic group, decarboxylation, and cyclisation of the side-chain of the amino acid to provide the cyclopentenyl moiety. This process

is summarised in scheme 1 and is biosynthetically unique. One particularly interesting feature of the biosynthesis of XVI is the possibility that the exocyclic double bond is isomerised during biosynthesis to the thermodynamically less stable configuration.

Scheme 1

Four of these isocyanides have been synthesised; dermadin (XV, Fukuyama and Yung 1981), XVI (Baldwin et al. 1984) XVII and XVIII (Baldwin et al. 1985), the first of these being particularly elegant (scheme 2).

Scheme 2

Gliotoxin (XXI) was one of the first fungal metabolites discovered to have antibiotic action (Weindling 1934; Bell et al. 1958) and was the first compound demonstrated to have the interesting disulphide bridge across a dioxopiperazine ring (Lowe et al. 1966). Interest in the chemistry of this compound has revived recently since it has been shown that it inhibits the immune system of mammals at 50 ng ml^{-1} and organisms capable of producing it have been isolated from the circulatory fluids of patients with the so-called autoimmune deficiency syndrome (Müllbacher and Eichner 1984). Among related compounds is gliovirin (XXV) where the sulphur bridge spans 5 atoms, probably a more stable configuration, analogous to the anisyl thioacetal derivatives used so successfully by Kishi in his synthesis of gliotoxin (Kishi et al. 1972). Its only known analogue as a natural product is sporidesmin C (Hodges and

Shannon 1966). The biosynthesis of these sulphur compounds has been exhaustively examined and has been reviewed on numerous occasions (see e.g. Leigh and Taylor 1976).

Polypeptide metabolites other than proteins, of Gliocladium spp., Hypocrea spp. and Trichoderma spp.

The peptide metabolites of these fungi can be divided into two groups - those produced by *Trichoderma polysporum* i.e. XXXIV and XXXVI, and all of the others. This may be a chemotaxonomic basis for the reclassification of *T. polysporum* as *Tolypocladium inflatum* (Traber *et al.* 1982). The structure of the cyclosporins is based

XXXIV
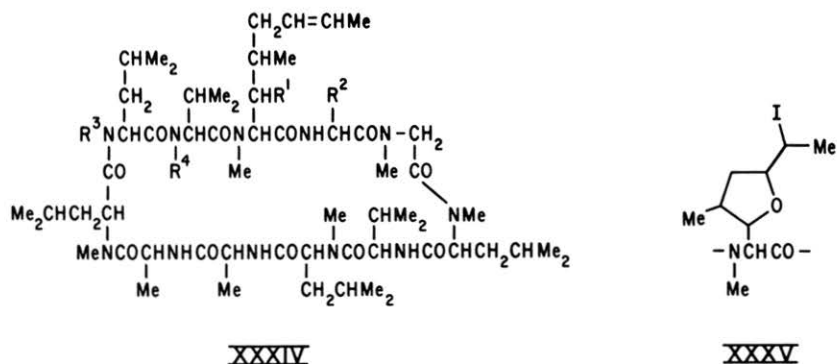
XXXV

on x-ray crystallography of the iodo derivative XXXV in which the 3-hydroxyl group of the unsaturated 4-methylcaprylic acid side-chain and iodine have added to the double bond (Petcher *et al.* 1976). This same hydroxyl group participates in a rearrangement involving the 2-methylamino group of this C_9 amino acid whereby a depsipeptide is produced; the lactone being generated with the proximal valyl residue. No details of the toxicity of such depsipeptides have been revealed. A synthesis of cyclosporin A (XXXIV, R^1-=OH, R^2=Et, R^3=R^4=Me) and its enantiomer cyclosporin H has been reported (Wenger 1984).

XXXVI

XXXVII

XXXVIII

XXXIX
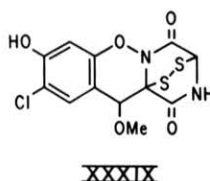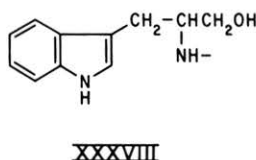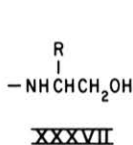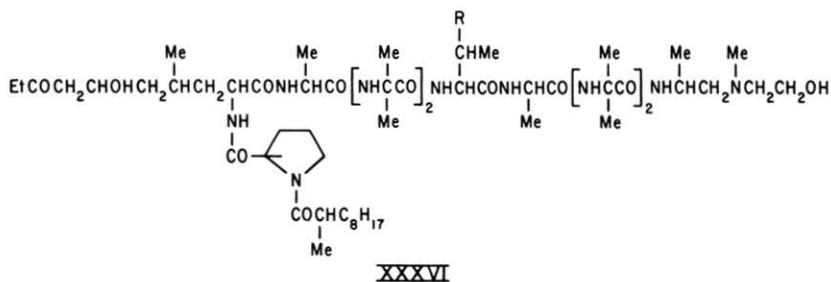
Table V Polypeptide antibiotics produced by *Hypocrea peltata*, *Gliocladium deliquescens* and *Trichoderma* spp.

Trivial Name	Producing Organism	Structure	m.p.	$[\alpha]_D$	References
Cyclosporin A	T. polysporum	XXXIV, R^1=OH, R^2=Et, R^3=R^4=Me	148-51°	-244°	Ruegger et al., (1976)
Cyclosporin B	- do -	XXXIV, R^1=OH, R^2=R^3=R^4=Me	149-52°	-244°	Traber et al., (1977)
Cyclosporin C	- do -	XXXIV, R^1=OH, R^2=CHOHMe, R^3=R^4=Me	152-5°	-238°	Ruegger et al., (1976)
Cyclosporin D	- do -	XXXIV, R^1=OH, R^2=CHMe$_2$, R^3=R^4=Me	148-51°	-255°	Traber et al., (1977)
Cyclosporin E	- do -	XXXIV, R^1=OH, R^2=Et, R^3=Me, R^4=H	142-3°	-179°	Traber et al., (1982)
Cyclosporin F	- do -	XXXIV, R^1=H, R^2=Et, R^3=R^4=Me	183-4°	-290°	
Cyclosporin G	- do -	XXXIV, R^1=OH, R^2=CHMe$_2$ R^3=R^4=Me	196-7°	-245°	
Cyclosporin H	- do -	XXXIV, R^1=OH, R^2=Et, R^3=R^4=Me	162-5°	-177°	
Cyclosporin I	- do -	XXXIV, R^1=OH, R^2=CHMe$_2$, R^3=H, R^4=Me	137-40°	-177°	
Trichotoxin	T. viride	See Table VI	187°		Hou et al., (1972); Brückner et al., (1979)
Alamethicin	T. hamatum	- do -	275-9°	-5°	Upjohn Co., (1969); Pandey et al., (1977)
Gliodeliquescin	G. deliquescens	- do -	260°		Brückner & Przybylski (1984)
Hypelcin AI	H. Peltata	- do -	265-6°	-17°	Fujita et al., (1979, 1984)
Hypelcin AII	- do -	- do -	254-6°	-1°	
Hypelcin AIII	- do -	- do -	256-8°		
Hypelcin AIV	- do -	- do -	259-61°		
Paracelsin	T. reesei	- do -	253-5°	-19.5°	Brückner et al., (1984)
Suzukacillin	T. viride	- do -	250°	-85.7°	Ooka et al., (1966); Katz (1983)
Trichorzianine	T. harzianum	- do -	253-4°	-25°	Davoust et al., (1983); Bodo et al., (1985)
Trichopolyn I	T. polysporum	XXXVI, R=Et	114-6°		Fuji et al., (1978)
Trichopolyn II = tricholides	- do -	XXXVI, R=Me			Fujita et al., (1981)

Table VI Tentative structures of 2-methylalanine polypeptide antibiotics

Trivial name	Position of amino acid residue from N-terminal end of the chain																				
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
Alamethicin I	Ac	Aib	Pro	Aib	Ala	Aib	Ala	Gln	Aib	Val	Aib	Gly	Leu	Aib	Pro	Val	Aib	Aib	Glu	Gln	P
II							Aib														
Gliodeliquescin			Ala																Gln		
Paracelsin A			Ala										Aib						Gln		
B			Ala							Leu			Aib						Gln		
C			Ala				Aib						Aib						Gln		
D			Ala				Aib			Leu			Aib						Gln		
Suzukacillin I			Ala							Aib									Gln		
II			Ala				Aib			Leu								Iva	Gln		
Hypelcin I							Aib			Leu			Aib						Gln		L
II										Leu			Aib						Gln		L
III							Aib			Leu			Aib						Gln		-
IV							Aib			Ile			Aib						Gln		L
Trichotoxin E			Gly		Leu		O			Aib		Ala	Ala			Leu			O		V
F			Gly		Leu		O			Aib	Ala	Ala	Ala			Leu		Iva	O		V
G			Gly		Leu		O			Aib		Ala	Ala			Leu			O		V
Trichorzianine AIIc			Ala	0			Aib			Aib		Ser						Ile	Gln		T

Abbreviations: Aib = 2-methylalanine; Iva = 2-ethylalanine; P = XXXVII, R=CH$_2$C$_6$H$_5$; L = XXXVII, R=CH$_2$CHMe$_2$; V = XXXVII, R = CHMe$_2$; T = XXXVIII; O = residue missing; - = unkno O Ac = CH$_3$CO-. All other amino acid abbreviations are standard. A blank indicates the amino acid cited at the top of the column.

By contrast, the structures of the remaining metabolites summarised in Tables V and VI are less secure. All of the compounds given in the Tables are in fact complex mixtures analogous to the cyclosporins (Brewer et al. 1979, Shaw and Taylor 1986). In the case of alamethicin, x-ray crystallography of the mixture of metabolites (Fox and Richards 1982) has provided impressive support of the structure proposed by Pandey et al. 1977) based on degradative chemistry and mass spectroscopy. The data given in Table VI reveals that about 10 i.e. half of the positions in the chain are invariate and only at position 10 are there more than 2 or 3 variations. Such variations are common in other congeneric peptide metabolites (Taylor 1970) especially if the known relationship of valine with 2-methylalanine (Ooka and Takeda 1974) is taken into account. There have been 4 totally independent attempts to synthesise the proposed alamethicin sequence (Nagaraj and Balaram 1981a, Gisin et al. 1981, Balasubramanian et al. 1981, Schmitt and Jung 1985). The results of this prodigious effort have been summarised by the latter authors, whose synthesis uniquely considered the stereochemical complexities of the procedure. All four products had different physical properties, only two were reported to have biological activity - if the detergent properties of all such lipophilic peptides are not considered. It must be emphasised that these discrepancies indicate non-trivial chemical problems associated with the determination of purity and hence identity of such large molecules. The composition and proportions of peptide metabolites is greatly influenced by the fermentation conditions (Brewer et al. 1979) and it is therefore possible that many of the assemblies of congeners given in Tables V and VI contain identical components. However, a test of this supposition will require much better methods of separation than those currently available.

A number of other peptide metabolites of this group of fungi have been reported but at present have not been characterised to the same extent as those in Table V. These include antibiotic 1037 ([α]$_D$-8°, Ooka 1977) produced by *T. viride* and a phytotoxic substance 11313 (m. p. 330-1°) produced by *Gliocladium zaleskii* (Nazarova and Zakharova 1982).

Biosynthetic studies have been made in the cases of alamethicin and suzukacillin. Good evidence that the biosynthesis was not ribosomal, but analogous to that of valinomycin or gramicidin A was obtained by Reusser (1966), and much later by Kleinkauf and Rindfleisch (1975). It has been proposed that the biosynthesis starts at the N-acetyl 2-methylalanyl N-terminal moiety and thence proceeds stepwise by addition of amino acid residues as activated thio esters (Mohr and Kleinkauf 1978). The mechanism of chain termination with a β-amino alcohol is unknown but the latter authors have provided some information about the generation of this C-terminal residue.

Toxicity of metabolites of Gliocladium spp., Hypocrea spp., and Trichoderma spp.

No attempt is made in this section to give a complete account of all the toxicological studies to be found in the literature on the compounds described in Tables II-V. Table VII is an attempt to reduce this literature, drastically, so that comparisons can be made. In general organisms have been selected to appear in Table VII because they are commonly used in toxicological studies, and to some extent comparisons are permissable. However, many toxicological phenomena cannot be conveniently tabulated and these matters are presented in the following text where each group of metabolites (as in Tables II-V) is discussed in turn. Problems of synergy are appreciated but not considered.

Polyketide metabolites (Table II) Very little is known of the toxicological properties of benzoquinones such as aurantiogliocladin (I, R=Me, R'=R''=OMe). Of course benzoquinone is known to be irritant and the recommended safety level of its vapour is about 0.1 p.p.m. (Sax 1968). The m. p. of benzoquinone is 115° and it is therefore

Table VII Toxicities of metabolites of *Hypocrea* spp., *Gliocladium* spp., and *Trichoderma* spp.

Metabolite	Structure	In vitro antimicrobial activity (μg ml^{-1}) Antibact. Gram+	Gram-	Antifung.	Toxicity Growth of mammalian cells μg ml^{-1}	LD$_{50}$ in Mammals. Route of Admin. (mg kg^{-1})		References
Aurantiogliocladin	I, R=Me, R′=R″=OMe	200[a]	400[b]	50[A]				Brian et al., (1951)
Glioresein	I, dihydro, R=Me R′=R″=OMe	200[a]	400[b]	400[A]				- do -
Dehydroacetic acid	XXX	3000[g]	2000[h]	500[E]		oral	1000[R]	Spencer et al., (1950)
Gliocladic acid	V				active	oral	200[M]	Itoh et al., (1982)
Heptelidic acid	VI	25[c]	0.4[D]		0.25	i.p.	31.5[M]	Itoh et al., (1980)
Trichodermin	IX, R=R‴=H, R′=Me, R″=OAc			+[B]		s.c.	500[M]	Yamamoto et al., (1969)
T$_2$-toxin	IX, R=OCOCH$_2$CHMe$_2$, R′=CH$_2$OAc, R″=OAc, R‴=OH			30[E]	0.03	oral	4[M]	Ueno et al., (1973); Marasas et al., (1969); Schappert and Khachatourians (1983)
Viridin	X, Y=O			0.006[A]				Brian et al., (1946)
Isonitrin D	XI	200[a]	200[b]	12.5[B]				Fujiwara et al., (1982)
Isonitrin B	XII	200[a]	100[b]	200[B]		i.p.	300[M]	- do -
Isonitrin A	XIII	12.5[a]	1.56[b]	6.25[B]		i.p.	160[M]	- do -
Trichoviridin	XIV	100[a]	6.26[b]	25[B]		i.p.	100[M]	- do -
Dermadin	XV	2.3[e]	3.13[b]	200[B]		i.p.	240[M]	- do - Brewer et al., (1982)
	XVI	2.5[e]	1.5[f]	200[B]		i.p.	20[M]	Fujiwara et al., (1982)
Gliotoxin	XXI	0.8[a]	18.7[b]	100[B]	0.1	oral	50[M]	Brewer et al., (1966)
						i.p.	50[M]	Taylor (1971); Allen et al., (1954); Johnson et al., (1943)

Compound	Structure					Route	Dose	Reference
Gliovirin	XXV			0.06^C				Howell and Stipanovic (1983)
Trichorin A			50*					Katayama et al., (1977)
Cyclosporin A	XXXIV, R'=OH, R²=Et, R³=R⁴=Me			3^D	4	oral	2000^M	Traber et al., (1977); Gorden and Singer (1979); Borel et al., (1976)
Cyclosporin B	XXXIV, R¹=OH, R²=R³=R⁴=Me			3^D				- do -
Cyclosporin C	XXXIV, R¹=OH, R³=Me, R⁴=Me, R²=CHOHMe			1^D				- do -
Cyclosporin D	XXXIV, R¹=OH, R³=Me, R⁴=Me, R²=CHMe₂			1^D				- do -
Alamethicin	See Table VI	31^c	200^i	100^F		oral	80^M	Meyer and Reusser (1967); Brewer et al., (1979)
Hypelcins	- do -	25^a	100^b	100^G				Fujita et al., (1984b)
Paracelsins	- do -					i.p.	5^M	Brückner et al., (1984)
Suzukacillin	- do -	10^a		100^D				Ooka et al., (1966)
Trichotoxin	- do -	1000^g				i.p. / oral	4.36^M / 600^M	Hou et al., (1972) - do -
Trichorzianine	- do -		$+^H$					Merlier et al., (1985)
Trichopolyns	XXXVI	6.25^a	100^b	6.25^B		i.p.	5^M	Fuji et al., (1978)

Abbreviations: Bacteria: a=Bacillus subtilis, b=Escherichia coli, c=Streptococcus faecalis, d=Bacterioides fragilis, e=Micrococcus luteus, f=Bacterioides succinogenes, g=Staphylococcus aureus, h=Salmonella typhosa, i=Selenomonas ruminantium. Fungi: A=Botrytis allii, B=Candida albicans, C=Pythium ultimum, D=Aspergillus niger, E=Saccharomyces cerevisiae, F=Blastomyces dermatitidus, G=Trichophyton rubrum, H=Botrytis cinerea. Animals: M=Mice, R=rats. *=organism not given; +=concentration unknown.

possible that the more volatile benzoquinone metabolites (I, m. p. 63°, Table 2) could achieve high concentrations in enclosed spaces should building structural material become colonised with isolates of *Gliocladium roseum* capable of their production. The orcinol derivatives (Pettersson 1965) are probably much less toxic since the LD_{50} of orcinol in mice is known to be 722 mg kg^{-1} (Veldre et al., 1971). The anthraquinones (XXXII) are generally regarded as non-toxic though emodin (XXXII, R=R^1=R^3=OH, R^2=Me) is thought to be one of the active ingredients in traditional purgatives.

The pyrone derivatives (IV, x=CH$_2$-CH$_2$, CH=CH) were first isolated during investigations of the odors associated with these fungi e.g. in brackish water (Kikuchi et al. 1974) and in the latter case to find the agent capable of initiating oospore formation in *Phytophthora*. However there has been a recent claim (Merlier et al. 1985) that the C_5H_{11} pyrone is fungicidal. Dehydroacetic acid (XXX) has some claim as a general antiseptic in view of its bactericidal action (Spencer et al. 1950) and low toxicity, but it has not been used because of the superior properties of detergents such as cetyl trimethylammonium halide.

Terpene metabolites (Table III) Avellaneol (III) has been reported (Nair et al. 1982) to be active against PS 388 lymphocytic leukemia in mice, but no experimental details were given.

Gliocladic acid (V) and heptelidic acid (VI) were discovered during investigations of the biological activity of a number of isolates of *Gliocladium virens, Trichoderma viride,* and *Chaetomium globosum* from soil. Gliocladic acid at a dose of 3 mg kg^{-1} in female mice inhibited the growth of sarcoma-37 by 46% and was less toxic than the related metabolite heptelidic acid (Itoh et al. 1982). The latter acid has a noticeable specificity for inhibition of growth of some anaerobic bacteria though the range of bacteria that are susceptible is narrower than that affected by the isocyanide XVI.

Trichodermin (IX, R=R'''=H, R'=Me, R''=OAc) and T$_2$-toxin (IX, R=OCOCH$_2$CHMe$_2$, R'=CH$_2$OAc, R''=OH) represent the extremes of toxicity found in more than 100 trichothecins now known to be produced by fungi. In all cases that have been examined in detail large numbers of congeneric trichothecins have been found (e.g. Greenhalgh et al. 1984), and it therefore seems likely that the *Trichoderma* spp. that have been reported to produce trichodermin and T$_2$-toxin also produce a range of trichothecins in low concentration. It can be seen from Table VII that there are more than two orders of magnitude in the acute toxicity of trichoderm and T$_2$-toxin in mice. Thus the precise toxicity of the mixture of metabolites produced by a particular isolate will depend on the toxicity *of the mixture*. The factors that govern the composition of such mixtures are unknown. The literature devoted to the toxicity of T$_2$-toxin is very large (for a general review see Ueno 1983) since it has been implicated in mycotoxicoses in farm animals (Mirocha 1983) and in alimentary toxic aleukia in man (Joffe 1974). In general trichothecins have little or no antibacterial properties, but inhibit the growth of fungi and other eukaryotic cells. Thus rapidly growing cells such as B and T lymphocytes are particularly susceptible and there is a growing literature on the effect of T$_2$-toxin on the mammalian immune system. The reader is referred to one of the reviews cited above for further details on the toxicology of this and other trichothecins.

Viridin (X, Y=0) and viridiol (X, Y=H, OH) are unusual steroid derivatives that are very active inhibitors of fungal spore germination (Brian et al. 1946). The germination of spores of *Collectotrichium lini* and *Fusarium coeruleum* was inhibited at 3 ng ml^{-1} and the germination of spores of *Cladosporium herbarum, Fusarium culmorum, Penicillium digitatum, P. notatum,* and *Stemphyilium* spp. at 0.2 μg ml^{-1}. Viridin was only fungicidal to the latter fungus at 50 μg ml^{-1}. No data on the mammalian toxicity of viridin has been published.

Non-polypeptide metabolites derived from α-amino acids

From a toxiciological point of view these metabolites fall into two groups - the cyclo-pentenylisocyanides and the epidithiodioxopiperazines.

CycloPentenylisocyanides. The first report of these compounds as metabolites occurred about 8 years ago (Nobuhara *et al.* 1976) and work on their toxicity has been hampered by their instability. However in the period that has elapsed since 1976 they have emerged as very common metabolites of *Trichoderma hamatum* (Brewer and Taylor 1981) and several other *Trichoderma* spp. (Fujiwara *et al.* 1982). They have marked bacteriostatic properties but the bacterial spectrum that is susceptible is unusual. The growth of Gram + bacteria except for *Sarcina lutea* is inhibited at concentrations greater than 100 μg ml^{-1}, but Gram - bacteria and particularly obli-gately anaerobic bacteria are inhibited in the concentration range 0.1-10 μg ml^{-1}. Bacteria that digest cellulose are very susceptible, especially to the unstable com-pound XVI. Thus cellulose digestion is inhibited by XVI in *Ruminococcus albus* at 5 μg ml^{-1}; in *R. flavofasciens* at 6 μg ml^{-1} and in *Bacterioides succinogenes* at 1-2 μg ml^{-1} (Liss *et al.* 1985). In general the genus *Bacterioides* is very susceptible to this antibiotic. At minimum inhibitory concentrations of XVI its activity is reversed by addition of approximately equimolar amounts of nickelous ion (Brewer *et al.* 1986) and it has been suggested that the mode of action of these compounds lies in their ability to co-ordinate with Ni cofactors (Whitman and Wolfe 1980) implicated in, for example, the reduction of pyruvate to propionate or formaldehyde to methane. The acute toxicities of these isocyanides to mice is given in Table VII (Fujiwara *et al.* 1982) and it can be seen that the toxicities of the various compounds very considerably. One of the most toxic, XVI, has been fed to lambs, intraruminally at a dose level of 5 mg kg^{-1} day^{-1} for 3 weeks without overt toxicity, apart from a slightly slower weight gain which could be attributed to an induced, reduced digestibility of the feed.

Epidithiodioxopiperazines. The toxicity of gliotoxin (XXI) has been known for more than 50 years, but early reports of its fungicidal activity were probably biased by the contamination of specimens with viridin. However Johnson *et al.* (1943) showed that gliotoxin was bacteriostatic at about 0.5 μg ml^{-1} against Gram + bacteria and at about 10 μg ml^{-1} against Gram - organisms. It inhibited the growth of *Penicillium italicum* at 100 μg ml^{-1}, *Rhizopus* sp. at 10 μg ml^{-1} and *Aspergillus niger* at 1 μg ml^{-1}. Its LD_{50} in mice, rats and rabbits was about 50 mg kg^{-1}, whether dosed orally, intraperitoneally, or intravenously. Two developments in its toxicology have occurred since this work was published. The first was the discovery that gliotoxin inhibited the growth of RNA virus in cell culture (Rightsel *et al.* 1964; Miller *et al.* 1968). A comprehensive review of its toxicology prior to 1970 has been published (Taylor 1971). The latest event is the report that gliotoxin inhibits phagocytosis of macrophage at 20-50 ng ml^{-1} and that at 0.1 μg ml^{-1} it abrogates induction of alloreactive cytotoxic T lymphocytes (Müllbacher and Eichner 1984). Since *Aspergillus fumigatus* is not only a known human pathogen but it is also known to produce gliotoxin (Menzel *et al.* 1944), there arises the question of whether the toxin is produced *in vivo*, and if so what effect this may have on the progress of an infectious agent(s). Gliovirin (Stipanovic and Howell 1982) which seems to be very similar to trichorin (Katayama *et al.* 1977) has a growth inhibiting effect on a very narrow range of fungi, though trichorin is known to have some effect on the growth of (unspecified) Gram - bacteria. The structure of gliovirin has some similarity to that of A30641 (XXXIX, though this structure has been questioned, Sakata *et al.* 1982), which has marked antifungal activity (Berg *et al.* 1976).

Non-protein polypeptide metabolites These compounds (Tables V and VI) fall into two groups - the cyclosporins, and linear peptides that contain several 2-methylalanine residues.

Cyclosporins. About 9 of these metabolites have been characterised but cyclos-porin A (XXXIV, R^1=OH, R^2=Et, R^3=R^4=Me) has been the main subject of toxicity studies.

These compounds have little or no bacteriostatic effect but as shown in Table VIII both cyclosporin A and cyclosporin C (XXXIV, R^1=OH, R^2=CHOHMe, R^3=R^4=Me) inhibit the growth of fungi and in some cases at low concentration (Dreyfuss et al.

Table VIII Growth inhibition of some fungi by cyclosporin A and cyclosporin C

Organism inhibited	Minimum Inhibitory Concentration (μg ml^{-1})	
	Cyclosporin A	Cyclosporin C
Rhodotorula rubra	100	100
Oospora lactis	31.6	100
Aspergillus niger	3	1
Curvularia lunata	1	1
Neurospora crassa	10	10
Anixiopsis stercoraria	100	100
Trichophyton quinckeanum	10	31.6

1976); this activity perhaps provides a rationale for the use of these compounds in the treatment of patients with immune deficiency. However the main toxicological properties of these compounds are their remarkable effects on the immune system of mammals. The literature on this subject is large and growing. Some indication of its size may be had from the facts that there are 149 references to this subject in the 10th collective index of Chemical Abstracts, but 70 references in the 6 month period (Vol. 101) July-December 1984. No attempt to review this literature is made - the reader can consult several excellent surveys e.g. Weil 1984, Thomson et al. (1984). Renal and/or hepatic and/or hemopoietic abnoramlities have been found in mice, rats, rabbits, dogs, chickens and monkeys at dose levels of about 25 mg kg^{-1} day^{-1}. In man this is about twice the dose used in immunosuppressent therapy. It may be concluded that the low concentrations of these compounds possibly present in the environment are not a toxicological hazard.

Alamethicin-like peptides. These compounds inhibit the growth of a wide range of bacteria and fungi. Representative examples are given in Table VII. It is possible that some of the discrepancies in the literature regarding the bacteriostatic effect of these metabolites is due to the fact that they diffuse slowly through agar. Thus the diameter of zones of inhibition depend, more critically than usual, on the time of diffusion before inoculation. In general the LD$_{50}$ in mice treated intraperitoneally with any of these compounds is about 5 mg kg^{-1}, but about 100 times this dose can be tolerated when it is administered orally. This also is probably due to slow diffusion and hence uptake through the wall of the gut. Paradoxically, the great interest that these compounds have evoked lies in their remarkable effects on membrane physiology. This subject has stimulated a great deal of interest and there are several excellent reviews available on the subject (e.g. Jung et al. 1979, Nagaraj and Balaram 1981b). In brief, these are amphiphilic molecules which differ from such trans-membrane carriers as valinomycin (where transport is dependent on the selective residence of a metal ion e.g. K$^+$ in the interannular space of the cyclic peptide) or gramicidin A (which induces a voltage independent dimeric channel) by inducing conductance which is exponentially dependent on the applied voltage. The channel structures (Fox and Richards 1982) are characterised by an hydrophilic interior and a hydrophobic exterior and are stabilised by an hydrated annulus of glutamine residues. A model for the mechanism of pore formation has been proposed by Jung and his coworkers (Boheim et al. 1983). Thus the mammalian toxicity of the metabolites is probably manifested by their effect on neuro-transmission, though their access to

such sensitive receptors is limited by their high molecular weight. In general they are not hydrolysed by peptidases and thus might progress through the gut unscathed, affecting the intestinal flora in a possibly deleterious way.

Miscellaneous antagonistic effects of Trichoderma spp. Mycologists have been interested in the phenomenon of soil fungistasis for more than 50 years and the suspicion that *Trichoderma* spp. were involved has been entertained by many workers (see e.g. Elad *et al.* 1980, Widden and Abitol 1980). Unambiguous experimental evidence for the phenomenon is however rare - Mitchell and Dix (1975) showed that the germination of *Trichoderma* spores was inhibited by sterile soil but by contrast Lewis and Papavizas (1984) found that *Trichoderma* spp. proliferated in soil when added as a mycelial culture. Dennis and Webster (1971b) have shown, by elegant photomicroscopy, that *Trichoderma* spp. can grow on the mycelium of other fungi and in the Soviet Union (Kanivets *et al.* 1940) increased yields of several crops have been claimed after infestation of soil with *Trichoderma lignorum*. Earlier work on the role of gliotoxin in soil fungistasis has been reviewed (Taylor 1971). In summary the use of *Trichoderma* spp. as agents in biocontrol systems has stimulated much work but little practical application has as yet emerged.

Methods and agents for the control of growth of Trichoderma and taxonomically related genera

A representative selection of compounds that have been claimed to retard the growth of these fungi is given in Table IX. The bulk of these compounds fall into the categories: fungicidal triazines (XL), benzimidazoles (XLI, see in addition Tabata and Kondo 1977), phenylurea/urethanes (XLIII, XLIV), thiourea/thiourethanes (XLVIII, LII) and insecticidal chlorinated hydrocarbons (XLV, XLVI, LIII). The number of compounds studied in each group is probably large but details of the concentrations at which inhibition was observed are hard to find. For example, among chlorinated compounds patent protection for compounds of the type $ROCH_2CH=CHCH_2Cl$ (R=Me, C_6H_5, Cass 1949) was obtained as antagonists of *Gliocladium fimbriatum* but there seems to have been no exploitation of this discovery. Similarly considerable work has been done on the effect of dichlorvos ($(MeO)_2POOCH=CCl_2$) on *Trichoderma viride* (Matsumora and Boush 1968) but I have been unable to find the minimum concentration of this insecticide that inhibits growth of the fungus. It seems to be generally held that chlorophenols preserve wood from all but superficial attack by these fungi (Lew and Wilcox 1981, Cserjesi and Rolf 1976) but I have been unable to find details of the relationship between structure and activity despite the known mammalian toxicity of these compounds (Sax 1968).

The importance of the preservation of wood has led to many studies of the antifungal effects of fumigation. Reference has already been made to the disastrous use of formaldehyde for this purpose; ethyl mercaptan has also been used (Kvasnikov *et al.* 1971) but had no effect on *Gliocladium salmonicolor* and only slight effect (at 0.6 μg ml^{-1}) on *Trichoderma lignorum*.

There remain a miscellaneous group of materials that have growth suppressive activity, at relatively high concentration; these include: manganous ion (at 0.5 mg ml^{-1}, Babich and Stotzky 1981), certain alkyloxyacetic acids ($ROCH_2CO_2H$, R=C_8H_{17}, C_9H_{19}, $C_{11}H_{23}$; 0.1 mg ml^{-1}, Gershon *et al.* 1979), a tetraene antibiotic (Chakrabarty and Chandra 1979), and certain α-naphthoquinones (0.1 mg ml^{-1}, Tripathi *et al.* 1980).

A further group of poorly defined materials include bacterial volatile metabolites (Moore-Landecker and Stotzky 1972) and hot water extracts of oak-bark - probably tannic acids and catechin (LIV, Yoshimoto *et al.* 1984). Finally there are reports of suppression of spore germination of *Trichoderma viride* by ozone (Hibben and Stotzky 1969); actinomycin D (0.1 mg ml^{-1}); cycloheximide (0.005 mg ml^{-1}) and 5-fluorouracil (0.01 mg ml^{-1}, Betina and Spisiakova 1976).

Table IX Compounds known to inhibit growth of *Hypocrea pilulifera*, *Gliocladium* spp. (G), and *Trichoderma* spp. (T)

| Trivial Name of Inhibitor	Chemical Structure	Susceptible Fungi	Min. Growth Inhib. Conc. (mg ml^{-1})	References
Atrazine	XL, R=Cl, R'=Et, R'=CHMe$_2$	T		Couch *et al.*, (1965)
			0.1	Stratton (1983)
Benomyl	XLI, R=CONHC$_4$H$_9$, R'=NHCO$_2$Me	G		Davet (1980)
		T. viride		- do -
		T. harzianum		Davet (1981)
		- do -		Cserjesi and Rolf (1976)
		T. virgatum		- do -
Benlate	- do -	T		Usui and Iida (1980)
Thiuram	LII	T		- do -
		T	0.3	Popescu (1979)
Butachlor	XLII, R'=Et, R^2=COCH$_2$Cl, R^3=CH$_2$OC$_4$H$_9$, R^4=H	T		Chen (1980)
Carbendazim	XL, R=H, R'=NHCO$_2$Me	G		Davet (1980)
		T. viride		- do -
2,4-Damine	?XLII, R'=R^4=Cl, R'=R^2=H, R^3=CH$_2$CO$_2$H	- do -	1	Pommer (1966)
Dalapon	2,2-dichloropropionic acid	- do -		Senior *et al.*, (1976)
DDT	XLV	- do -	0.03	Singh *et al.*, (1977)
	Dipropyleneglycol dibenzoate	T. longibrachiatum		Butz *et al.*, (1983)
Diuron	XLIII, R^1=R^2=Me, R^3=R^4=Cl	T. viride	10	Davis *et al.*, (1976)
Endrin	XLVI	- do -		Singh *et al.*, (1977)
		T		Patil *et al.*, (1970)

EPTL	$(C_3H_7)_2NCOSEt$	T. viride		Peeples (1972)
Fluometuron	XLIII, $R^1=R^2=Me$, $R^3=H$, $R^4=CF_3$	- do -	10	Davis et al., (1976)
Heptachlor	LIII	- do -	0.01	Singh et al., (1977)
	Hexachlorobutadiene	T. lignorum	1-10	Mukasheva (1976)
		G. verticilloides	1-10	- do -
Lindane	Benzene hexachloride	T. viride	0.03	Singh et al., (1977)
Linuron	XLIII, $R^1=Me$, $R^2=OMe$, $R^3=R^4=Cl$	- do -		Glad et al., (1981)
Methabenzthiazuron	XLVII	Hypocrea pilulifera	.059	Göttfert and Corte (1978)
Methylthiophanate	XLVII	T. viride		Davet (1980)
		G		- do -
Mexacarbate	XLII, $R^1=R^2=R^3=Me$, $R^4=CO_2NHMe$	T. viride	0.008	Benezet and Matsumura (1974)
MSMA	Monosodium methanarsenate	- do -	10	Davis et al., (1976)
Phenmediphan	XLIV, R=Me	- do -		Bellinck (1980)
	XLIV, R=H	- do -		- do -
	XLII, $R^1=R^2=H$, $R^3=CO_2Me$, $R_4=OH$	- do -		- do -
Permethrin	XLIX	- do -	0.1	Stratton (1983)
	Phenyl mercuric acetate	T	0.1	Popescu (1979)
Prometryn	XL, R=SMe, $R'=CHMe_2$	T. viride	1	Davis et al., (1976)
Sicarol	L	T		Anilkumar and Sastry (1979)
Simazine	XL, R=Cl, R'=Et	T		Couch et al., (1965)
Solanine	LI	T. viride	2	Patil et al., (1972)
Thiabendazole	XLI, R=H, R'=2-thiazolyl	T. harzianum		Cserjesi and Rolf (1976)
		T. virgatum		- do -
	Bu_3SnR (R=Cl, O, OAc)	T. viride		Selivokhin et al., (1974)
Trifluorin	XLII, $R^1=NO_2$, $R^2=R^3=C_3H_7$, $R^4=CF_3$	T. viride		Zayed et al., (1983)
Topsin M	XLVIII	T. lignorum	0.01-	Zoltanska (1984)
		T. koningii	0.001	- do -
		T. album	- do -	- do -
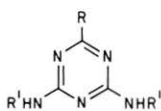
XL
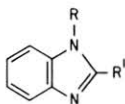
XLI
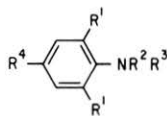
XLII
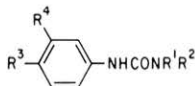
XLIII
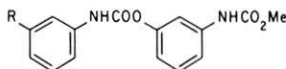
XLIV
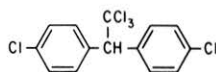
XLV
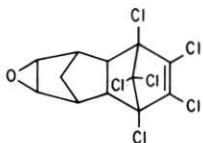
XLVI

XLVII

XLVIII

XLIX

L

LI

LII

LIII
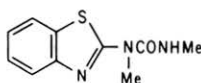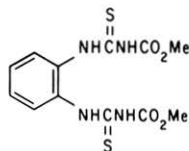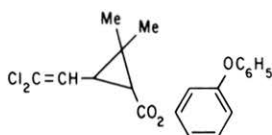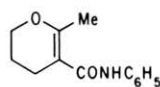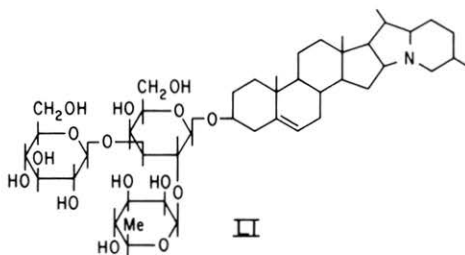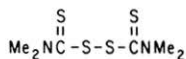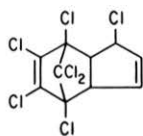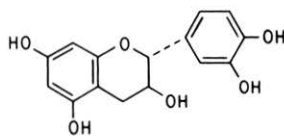
LIV

Conclusions

The data in the tables of this report demonstrate that the group of fungi that is its subject can be found in almost any environment of the planet; that they produce well-defined metabolites whose biological and chemical properties differ, but which include some of the most toxic substances hitherto described. Only under exceptional circumstances, e.g. when volatile metabolites accumulate in an enclosed space, when metabolites are produced in the course of an infectious process or when they are concentrated naturally in or during the manufacture of food, are acute, toxic manifestations patent. Such toxicity is rare, though an increasing number of examples are coming to light because of the use of better analytical facilities. In the case of long-term sub-clinical toxicity it is usually very difficult to associate cause and effect and therefore epidemiological phenomena of this sort are commonly overlooked. An appreciation of the latter problem and its implications for public heatlh is long overdue, but our ability to assess the importance of such chronic toxicities in society is hampered by inadequate analytical tools.

Until such methods become available our only recourse is to start with the population dynamics of this group of fungi making the assumption that the population density is related in some unknown way with the presence, composition, and concentration of its toxic metabolites. However this job can hardly be started because the taxonomy of this group (and related groups) of fungi fails to provide easy identification and hence classification. Assuming (as seems likely) that these problems can be solved there remains the question of the selective inhibition of fungal growth. Here the prognosis is not bright, because their elimination is probably undesirable, since there are those who believe them to be useful vectors in biological control methods, and perhaps more cogently, that elimination of a relatively benign component of the flora might result in its replacement with a virulent pathogen. Thus fungistatic agents are required, hopefully active at very low concentrations. The antifungal agents summarised in Table IX are effective at concentrations that are at least 4 orders of magnitude greater than e.g. the concentration of penicillin that inhibits the growth of *Streptococcus* spp. It can therefore be concluded that a considerable research effort is required to find antifungal agents that are effective in the concentration range 0.01 - 1 μg ml^{-1}. An examination of the dates of publications cited in Table IX indicates that the large economic losses due to fungal infestation of wood, wood products and cellulosic materials are in fact stimulating such a research programme, and on a world-wide scale. One hopes that the public health aspects of sub-acute mycotoxicoses, together with the growing realisation of their importance in animal production will provide further impetus for this research.

References

Abramova, E.A., Kanevskaya, I.G. and Bufetchikova, O. Yu. 1973. Effect of the degree of fungal damage on the properties of partially acetylated cellulose hydrate fibers. *Zh. Prikl. Khim*, 46: 1387-9.

Achilladelis, B.A., Adams, P.M. and Hanson, J.R. 1972. Studies in terpenoid biosynthesis. Part VIII. The formation of the trichothecane nucleus. *J. Chem. Soc*. (Perkin Trans. I). 1425-1428.

Adams, P.M. and Hanson, J.R. 1972. Sesquiterpenoid metabolites of *Trichoderma polysporum* and *T. sporulosum*. *Phytochemistry*, 11: 423.

Aguirre, F., Maldonado, O., Rolz, C., Menchu, J.F., Espinosa, R. and de Cabrera, S. 1976. Protein from waste. Growing fungi on coffee waste. *Chem. Abs.*, 85: 190592.

Allen, R.E., Shelton, R.S. and Van Campen, M.G. 1954. Antifungal agents. Some 3-imino-5-alkylmercapto-1,2,4-dithiazole salts. *J. Amer. Chem. Soc.*, 76: 1158-9.

Ananthasubramanian, L., Carey, S.T. and Nair, M.S.R. 1978. Metabolites of pyrenomycetes IX. Structure and absolute configuration of (+)-R-avellaneol, an antibiotic metabolite of Hypocrea avellanea. *Tet. Let.*, 3527-8.

Anilkumar, T.B. and Sastry, M.N.L. 1979. Effect of sicarol on the growth of Trichoderma sp. *Chem. Abs.*, 91: 118463.

Anisimov, A.A., Smirov, V.F., Semicheva, A.S. and Sheveleva, A.F. 1977. Protection of KD-type epoxy compounds from the effect of biological corrosion by introducing fungicidal additives into their compositions. *Chem. Abs.*, 87: 79467.

Arigioni, D., Cane, D.E., Müller, B. and Tamm, C. 1973. The mode of incorporation of farnesyl pyrophosphate into verrucarol. *Helv. Chim. Acta*, 56: 2946-9.

Babich, H. and Stotzky, G. 1981. Manganese toxicity to fungi: influence of pH. *Bull. Environ. Contam. Toxicol.*, 27: 474-480.

Balasubramanian, T.M., Kendrick, N.C.E., Taylor, M., Marshall, G.R., Hall, J.E., Vodyanoy, I. and Reusser, F. 1981. Synthesis and characterization of the major component of alamethicin. *J. Amer. Chem. Soc.*, 103: 6127-32.

Baldwin, J.E., Adlington, R.M. and Chondrogianni, J., Edenborough, M.S., Keeping, J.W. and Ziegler, C.B. 1985. Structure and synthesis of new cyclopentenyl isonitriles from *Trichoderma hamatum* (Bon.) Bain. aggr. HLX 1379. *J. Chem. Soc., Chem. Commun.*, 816-817.

Baldwin, J.E., Kelly, D.R. and Ziegler, C.B. 1984. The synthesis of a fungal isonitrile antibiotic via a novel radical addition-elimination reaction. *J. Chem. Soc., Chem. Commun.*, 133-134.

Bamburg, J.R. and Strong, F.M. 1969. Mycotoxins of the trichothecane family produced by *Fusarium tricinctum* and *Trichoderma lignorum*. Phytochemistry, 8: 2405-2410.

Behling, R.A. and Fischer, A.G. 1980. Formation of phenylalanylserine and cyclo-phenylalanylserine by protoplasts of *Gliocladium virens*. *Int. J. Biochem.*, 11: 457-458.

Bell, M.R., Johnson, J.R., Wildi, B.S. and Woodward, R.B. 1958. The structure of gliotoxin. *J. Amer. Chem. Soc.*, 80: 1001.

Belinck, C. 1980. Mineralization of phenmediphan and derivatives by Trichoderma viride. Immobilization of ¹⁴C residues. Effect on biological activity. *Chem. Abs.*, 92: 175750.

Benezet, H.J. and Matsumura, F. 1974. Factors influencing the metabolism of mexacarbate by microorganisms. *J. ag. Food Chem.*, 22: 427-430.

Berestetskii, O.A., Patyka, V.F. and Nadkernichnyi, S.P. 1978. Phytotoxic properties of fungi of the Trichoderma Pers. Genus. *Chem. Abs.*, 88: 148647.

Berg, D.H., Massing, R.P., Hoehn, M.M., Boeck, L.D. and Hamil, R.L. 1976. A30641, a new epidithiodiketopiperazine with antifungal activity. *J. Antibiotics*, 29: 394-397.

Bergman, O. and Nilsson, T. 1971. Reduction of microbial deterioration in outside chip storage by alkali treatment. *Chem. Abs.*, 74: 55422.

Berk, S. 1951. Effect of fungus growth on the tensile strength of polyvinyl chloride films plasticised with three plasticizers. *Chem. Abs.*, 45: 388f.

Betina, V. and Spisiakova, J. 1976. Suppression of photo-induced sporulation in Trichoderma viride by inhibitors. *Folia Microbiol.*, 21: 362-70.

Bilai, V.I. 1956. Trichoderma Pers. Volatile antibiotics in fungi of the genus *Trichoderma*. Microbiol. (Moscow) Eng. trans., 25: 458-465.

Bilai, V.I., Pidoplichko, M.M., Gutirya, V.S., Bukhalo, A.S., V'yun, G.A., Galick, P.M., Koval, E.Z., Masumyan, V. Ya. and Mil'ko, O.O. 1965. Petroleum hydrocarbons as the source of carbon for soil mycelial microscopic fungi. *Chem. Abs.*, 63: 7384.

Blight, M.M., Coppen, J.J.W. and Grove, J.F. 1968. The biogenesis from mevalonic acid, of the steroidal antifungal metabolite viridin. *Chem. Commun.*, 1117-8.

Bodo, B., Rebuffat, S., El Hajji, M. and Davoust, D. 1985. Structure of trichorzianine AIIIc, an antifungal peptide from *Trichoderma harzianum*. *J. Amer. Chem. Soc.*, 107: 6011-6017.

Boheim, G., Hanke, W. and Jung, G. 1983. Alamethicin pore formation: voltage-dependent flip-flop of α-helix dipoles. *Biophys. Struct. Mech.*, 9: 181-91.

Borel, J.F., Feurer, C., Gubler, H.U. and Stähelin, H. 1976. Biological effects of cyclosporin A: a new antilymphocytic agent. *Agents and Actions*, 6: 468-475.

Brewer, D., Calder, F.W., Jones, G.A., Tanguay, D. and Taylor, A. 1986. The effect of nickelous and other metal ions on the inhibition of rumen bacterial metabolism by 3-(3'-isocyanocyclopent-2-enylidene)-propionic acid and related isocyanides. *Appl. Environ. Microbiol.*, 51: 138.

Brewer, D., Feicht, A., Taylor, A., Keeping, J.W., Taha, A.A. and Thaller, V. 1982. Ovine ill-thrift in Nova Scotia. 9. Production of experimental quantities of isocyanide metabolites of *Trichoderma hamatum*. *Can. J. Microbiol.*, 28: 1252-1260.

Brewer, D., Hannah, D.E. and Taylor, A. 1966. The biological properties of 3.6-epidithiadiketopiperazines. Inhibition of growth of Bacillus subtilis by gliotoxins, sporidesmins and chetomin. *Can. J. Microbiol.*, 12: 1187-1195.

Brewer, D., Hanson, A.W., Shaw, I.M., Taylor, A. and Jones, G.A. 1979. A crystalline, toxic, peptide metabolite of *Trichoderma* spp. isolated from soil. *Experientia*, 35: 294-5.

Brewer, D. and Taylor, A. 1980. Ovine ill-thrift in Nova Scotia. 6. Quantitative description of the fungal flora of soils of permanent pasture. *Proc. N. S. Inst. Sci.*, 30: 101-133.

Brewer, D. and Taylor, A. 1981. Ovine ill-thrift in Nova Scotia. 7. Trichoderma hamatum isolated from pasture soil. *Mycopathol.*, 76: 167-173.

Brian, P.W. 1944. Production of gliotoxin by *Trichoderma viride*. Nature (Lond.), 154: 667.

Brian, P.W., Curtis, P.J., Hemming, H.G. and McGowan, J.C. 1946. The production of viridin by pigment forming strains of *Trichoderma viride*. *Ann. Appl. Biol.*, 33: 190-200.

Brian, P.W., Curtis, P.J., Howland, S.R., Jeffreys, E.G. and Raudnitz, H. 1951. Three new antibiotics from a species of Gliocladium. *Experientia*, 7: 266-267.

Brown, L.R. and Pabst, G.S. 1977. Biodegradation of stainless steel and aluminium alloys. *Chem. Abs.* 87: 188155.

Brückner, H., Graf, H. and Bokel, M. 1984. Paracelsin: characterization by NMR spectroscopy and circular dichroism, and hemolytic properties of a peptaibol antibiotic from the cellulolytically active mold *Trichoderma reesei*. Part B. *Experientia*, 40: 1189-1197.

Brückner, H., König, W.A., Greiner, M. and Jung, G. 1979. The sequences of the membrane-modifying peptide antibiotic trichotoxin A-40. *Angew. Chem.*, 91: 508-9.

Brückner, H. and Przybylski, M. 1984. Methods for the rapid detection, isolation and sequence determination of "peptaibols" and other aib-containing peptides of fungal origin. I. Gliodeliquescin A from *Gliocladium deliquescens*. *Chromatographia*, 19: 188-199.

Burge, H.A., Solomon, W.R., and Boise, J.R. 1980. Microbial prevalence in domestic humidifiers. *Appl. Environ. Microbiol.*, 39: 840-844.

Butz, R.G., Atallah, Y.H., Yu, C.C. and Calo, C.J. 1983. Environmental safety assessment of dipropyleneglycol dibenzoate. *Chem. Abs.*, 98: 138610.

Cass, O.W. 1949. Fungicide comprising 1-methoxy-4-chloro-2-butene U.S. 2462830; Fungicidal composition U.S. 2465061.

Chakrabarty, S. and Chandra, A.L. 1979. Antifungal activity of A-7 a new tetraene antibiotic. *Chem. Abs.*, 91: 754.

Chen, Yuh-Lin. 1980. Dissipation of herbicide Butachlor in water and soil. *Chem. Abs.*, 92: 168858.

Claydon, N., Grove, J.F. and Pople, M. 1985. Elm bark beetle boring and feeding deterrents from Phomopsis oblongata. *Phytochemistry*, 24: 937-943.

Collins, R.P. and Halim, A.F. 1972. Characterization of the major aroma constituent of the fungus *Trichoderma viride* (Pers.). *J. ag. Food Chem.*, 20: 437-438.

Colwell, R.R., Walker, J.D. and Nelson, Jr., J.D. 1974. Microbial ecology and the problem of petroleum degradation in Chesapeake Bay. *Chem. Abs.*, 80: 118116.

Cook, C.D. and Harrington, R. 1948. Growth of *Trichoderma* sp. on cork. *Product. Eng.*, 19: 107.

Couch, R.W., Gramlich, J.V., Davies, D.E. and Funderburk, H.H. 1965. The metabolism of atrazine and simazine by soil fungi. *Chem. Abs.*, 63: 3554h.

Cserjesi, A.J. and Rolf, J.W. 1976. Toxicity tests of some chemicals against certain wood-staining fungi. *Chem. Abs.*, 84: 100690.

Daines, R.H. 1937. Antagonistic action of *Trichoderma lignorum* on *Actinomyces scabies* and *Rhizoclonia solani*. *Am. Potato J.*, 14: 85-93.

Dao Cong Dan, Fanter, C. and Philipp, B. 1980. Enzymic and acid hydrolytic degradation of cross-linked cellulose samples. *Chem. Abs.*, 93: 169872.

Davet, P. 1980. Antagonistic activity and susceptibility to pesticides of some fungi associated with *Sclerotinia minor* sclerotia. *Chem. Abs.*, 92: 89175.

Davet, P. 1981. Effects of some pesticides on the colonization of a substrate by *Trichoderma harzianum* Rifai in the presence of other soil fungi. *Soil Biol. Biochem.*, 13: 513-517.

Davis, D.E., Pillai, C.G.P. and Truelove, B. 1976. Effects of prometryn, diuron, flumeturon and MSMA on Chlorella and two fungi. *Weed Sci.*, 24: 587-593.

Davoust, D., Bodo, B., Rebuffat, S. and Platzer, N. 1983. High field NMR study of antibiotic peptides: [1]H assignment of trichorzianine A1 spectra by 2D experiments. *Biochem. Biophys. Res. Commu.*, 116: 1-8.

Dennis, C. and Webster, J. 1971a. Antagonistic properties of species groups of Trichoderma. II. Production of volatile antibiotics. *Trans. Brit. Mycol. Soc.*, 57: 41-48.

Dennis, C. and Webster, J. 1971b. Antagonistic properties of species-groups of Trichoderma. III. Hyphal interaction. *Trans. Brit. Mycol. Soc.*, 57: 363-369.

Dinulescu, M. 1979. Mechanisms of action of micromycetes on wood. *Chem. Abs.*, 90: 100276.

Doi, N., Yamaguchi, J. and Kurata, K. 1972. Cellulases of the genus Hypocrea and its allies 2. *Chem. Abs.*, 77: 58530.

Dreyfuss, M., Harri, E., Hofmann, H., Kobel, H., Pache, W. and Tscherter, H. 1976. Cyclosporin A and C. New metabolites from Trichoderma polysporum (Link ex Pers.) Rifai. *Eur. J. Appl. Microbiol.*, 3: 125-133.

Elad, Y., Chet I. and Katan, J. 1980. Trichoderma harzianum: a biocontrol agent effective against Sclerotium rolfsii and Rhizotonia solani. *Phytopathology*. 70: 119-121.

Fox, R.O. and Richards, F.M. 1982. A voltage-gated ion channel model inferred from the crystal structure of alamethicin at 1.5 A° resolution. *Nature* (Lond.), 300: 325-330.

Fuji, K., Fujita, E., Takaishi, Y., Fujita, T., Arita, I., Komatsu, M. and Hiratsuka, N. 1978. New antibiotics trichopolyns A and B; isolation and biological activity. *Experientia*, 34: 237-9.

Fujita, T., Takaishi, Y., Okamura, A., Fujita, E., Fuji, K., Hiratsuka, N., Komatsu, M. and Arita, I. 1981. New peptide antibiotics, trichopolyns I and II, from *Trichoderma polysporum*. *J. Chem. Soc. Chem. Commun.*, 585-7.

Fujita, T., Takaishi, Y. and Shiromoto, T. 1979. New peptide antibiotic, hypelcin A, from Hypocrea peltata. *J. Chem. Soc., Chem. Commun.*, 413-414; *Chem. Pharm. Bull.*, 32: 2870.

Fujita, T., Takaishi, Y., Moritoki, H., Ogawa, T. and Tokimoto, K. 1984a. Fungal metabolites. I. Isolation and biological activities of hypelcins A and B (growth inhibitors against *Lentinus edodes*) from *Hypocrea peltata*. *Chem. Pharm. Bull.*, 32: 1822-8.

Fujita, T., Takaishi, Y., Takeda, Y., Fujiyama, T. and Nishi, T. 1984b. Fungal metabolites. II. Structural elucidation of minor metabolites, valinotricin, cyclonerodiol oxide, epicyclonerodiol oxide from *Trichoderma polysporum*. *Chem. Pharm. Bull.*, 32: 4419-4425.

Fujiwara, A., Okuda, T., Masuda, S., Shiomi, Y., Migamoto, C., Sekine, Y., Tazoe, M. and Fujiwara, M. 1982. Fermentation, Isolation and Characterization of isonitrile antibiotics. *Agric. Biol. Chem.*, 46: 1803-1809.

Fukuyama, T. and Yung, Y.M. 1981. Total synthesis of (±) methyl 3-(3-isocyano-6-oxabicyclo[3,1,0]hex-2-en-5-yl)-2-propenoate. *Tet. Let.*, 3759-60.

Gams, W. 1971b. Tolypocladium, eine hypomycetengattung mit geschwollenen phialiden. *Personnia*, 6: 185-191.

Gams, W. 1971a. Cephalosporium artige Schimmelpilze. Gustov Fischer Verlag, Stuttgart, p. 19.

Gatenback, S. 1958. Incorporation of labelled acetate in emodin in *Penicillium islandicum*. *Acta Chem. Scand.*, 12: 1211-1214.

Gauze, G.F., Terekhova, L.P., Maksimova, T.S., Brazhnikova, M.G., Fedorova, G.B. and Borisova, V.N. 1983. Screening of new antibiotics from a group of cyclosporins. *Antibiotiki*, 28: 243-5.

Gershon, H., Shanks, L. and de Angelis, A. 1979. Antifungal properties of n-alkoxyacetic acids and their methyl esters. *J. Pharm. Sci.*, 68: 82-84.

Gisin, B.F., Davis, D.G., Borowska, Z.K., Hall, J.E. and Kobayashi, S. 1981. Synthesis of the major component of alamethicin. *J. Amer. Chem. Soc.*, 103: 6373-7.

Glad, G., Goeransson, B., Popoff, T., Theander, O. and Tortenssen, N.T.L. 1981. Decomposition of linuron by fungi isolated from soil. *Swed. J. Agric. Res.*, 11: 127-134.

Godtfredsen, W.O. and Vangedal, S. 1965. Trichodermin, a new sesquiterpene antibiotic. *Acta Chem. Scand.*, 19: 1088-1102.

Golder, W.S. and Watson, T.R. 1980. Lanosterol derivatives as precursors in the biosynthesis of viridin. Part 1. *J. Chem. Soc.*, (Perkin Trans. I), 422-425.

Göttfert, J. and Korte, F. 1978. Wachstum von Hypocrea cf. pilulifera Webster St. Con. unter verschiedensen Kulterbedingunger in anwesenheit von Methabenzthiazuron. *Chemosphere*, 7: 881-92.

Gordon, M.Y. and Singer, J.W. 1979. Selective effects of cyclosporin A on colony-forming lymphoid and myeloid cells in man. *Nature* (Lond.), 279: 433-4.

Greenhalgh, R., Meier, R., Blackwell, B.A., Miller, J.D., Taylor, A. and ApSimon, J.W. 1984. Minor metabolites of *Fusarium roseum* (ATCC 28114). *J. ag. Food Chem.*, 32: 1261-4.

Griffin, G.J.L. and Mivetchi, H. 1977. Biodegradation of ethylene/vinyl acetate copolymers. *Chem. Abs.*, 87: 23921.

Grove, J.F., McCloskey, P. and Moffatt, J.S. 1966. Viridin. Part V. Structure. *J. Chem. Soc.* (C), 743-747.

Grove, J.F., Moffat, J.S. and Vischer, E.B. 1965. Viridin. Part I. Isolation and characterization. *J. Chem. Soc.* (C), 3803-3811.

Gudin, C. and Chater, K.W.A. 1977. Isolation of Trichoderma hamatum growing on ferric hydroxide mud impregnated with gas-oil. *Environ. Pollut.*, 14: 1-4.

Han, Y.W. and Anderson, A.W. 1975. Semi-solid fermentations of rye-grass straw. *Appl. Microbiol.*, 30: 930-4.

Hanson, A.W., McAlees, A.J. and Taylor, A. 1985. Ovine ill-thrift in Nova Scotia. Part 10. Palladium and rhodium complexes as reagents in the investigation of isocyanide metabolites of *Trichoderma hamatum*. *J. Chem. Soc.*, (Perkin Trans. I), 441-446.

Hanson, J.R. and O'Leary, M.A. 1981. New piperazinedione metabolites of *Gliocladium deliquescens*. *J. Chem. Soc.* (Perkin Trans. I), 218-220.

Hanson, J.R. and Wadsworth, H.J. 1979. Biosynthesis of demethoxyviridin. *J. Chem. Soc. Chem. Commun.*, 360-1.

Henderson, M.E.K. and Duff, R.B. 1963. The release of metallic and silicate ions from minerals, rocks and soils by fungal activity. *J. Soil Sci.*, 14: 236-46.

Hibben, C.R. and Stotzky, G. 1969. Effects of ozone on the germination of fungus spores. *Can. J. Microbiol.*, 15: 1187-1196.

Hodges, R. and Shannon, J.S. 1966. The isolation and structure of sporidesmin C. *Aust. J. Chem.*, 19: 1059-66.

Hou, C.T., Ciegler, A. and Hesseltine, C.W. 1972. New mycotoxin, trichotoxin A, from *Trichoderma viride* isolated from southern leaf blight-infected corn. *Appl. Microbiol.*, 23: 183-185.

Howell, C.R. and Stipanovic, R.D. 1983. Gliovirin, a new antibiotic from *Gliocladium virens*, and its role in the biological control of *Pythium ullimum*. *Can. J. Microbiol.* 29: 321-324.

Hutchinson, S.A. and Cowan, M.E. 1972. Identification and biological effects of volatile metabolites from cultures of *Trichoderma harzianum*. *Trans. Brit. Mycol. Soc.*, 59: 71-77.

Hussain, S.A., Noorani, R. and Qureshi, I. 1975. Microbial chemistry. Part I. Isolation and characterization of gliotoxin, ergosterol, palmitic acid and mannitol metabolic products of *Trichoderma hamatum* Bainier. *Pak. J. Sci. Ind. Res.*, 18: 221-223.

Igaue, I. 1966. Fungal enzymes active in degrading barley β-glucans. *Chem. Abs.*, 65: 961.

Itoh, Y., Kodama, K., Furuya, K., Takahashi, S., Haneishi, T., Takiguchi, Y. and Arai, M. 1980. A new sesquiterpene antibiotic, heptelidic acid: producing organisms, fermentation, isolation and characterization. *J. Antibiotics*, 33: 468-478.

Itoh, Y., Takahashi, S. and Arai, M. 1982. Structure of gliocladic acid. *J. Antibiotics*, 35: 541-2.

Jackson, R.B. 1973. Metabolism of allyl alcohol by Trichoderma viride. *J. Gen. Appl. Microbiol.*, 19: 41-54.

Joffe, A.Z. 1974. Toxicity of *Fusarium poae* and *F. sporotrichioides* and its relation to alimentary toxic aleukia. In Mycotoxins Ed. I. F. H. Purchase. Elsevier, Amsterdam, 229-262.

Johnson, J.R., Bruce, W.F. and Dutcher, J.D. 1943. Gliotoxin, the antibiotic principle of Gliocladium fimbriatum. I. Production, physical and biological properties. *J. Amer. Chem. Soc.*, 65: 2005-2009.

Jung, G., Brückner, H. and Schmidt, H. 1979. Properties of the membrane modifying polypeptide antibiotics alamethicin and trichotoxin A-40. *Struct. Act. Nat. Pept.*, Proc. Fall Meet. Ges. Biol. Chem., 75-114.

Kamal, A., Akhtar, R. and Qureshi, A.A. 1971. Biochemistry of microorganisms. XX. 2,5-Dimethoxybenzoquinone, tartronic acid, itaconic acid, succinic acid, pyrocalciferol, epifriedelinol, lanosta-7,9(11),24-triene-3β, 21-diol, trichodermene A, methyl 2,4,6-octatriene and cordycepic acid, Trichoderma metabolites. *Pak. J. Sci. Ind. Res.*, 14: 71-78.

Kanivets, I.I., Khariton, E.G. and Tul'chinskaya, E.M. 1940. Increased yield of sugar-beet, oats and lupine by soil infected with *Trichoderma lignorum*. *Microbiology* (USSR), 9: 143-51.

Katayama, T., Minato, H., Ishi, K. and Kondo, E. 1977. A new antibiotic, trichorin A. *J. Antibiotics*, 30: 430-431.

Kawasaki, C. and Ito, Y. 1966. Hydrolysis of chitin by fungal enzyme preparations. *Chem. Abs.*, 64: 20095.

Katz, E. 1983. Suzukacillin A: Sequenzierung und Konformationsuntersuchungen eines membranmodifizierten Eikosapeptids, Thesis. Tubingen, W. Germany.

von Kerner-gang, W., and Hoffmann, H. 1982. Untersuchungen zum Verhalten von Schimmelpilzen gegenüber Klebstoffen für Holzwerkstoffe. *Material und Organ.*, 17: 253-268.

Khimerik, T. Yu and Koval, E.Z. 1977. Study of fungal resistance of some road building materials. *Mikrobiol. Zh.* (Kiev), 39: 84-87.

Kikuchi, T., Mimura, T., Harimaya, K., Yano, H., Arimoto, T., Masada, Y. and Inoue, T. 1974. Volatile metabolite of aquatic fungi. Identificaton of 6-pentyl-α-pyrone from Trichoderma and Aspergillus Species. *Chem. Pharm. Bull.*, 22: 1946-1948.

Kirby, G.W., Robins, D.J., Sefton, M.A. and Talekar, R.R. 1980. Biosynthesis of Bisdithiobis-(methylthio)-gliotoxin, a new metabolite of *Gliocladium deliquescens*. *J. Chem. Soc.*, (Perkin Trans. I), 119-121.

Kishi, Y., Fukuyama, T. and Nakatsuka, S. 1972. A new method for the synthesis of epidithiodiketopiperazines. *J. Amer. Chem. Soc.*, 95: 6490-6492.

Kleinkauf, H. and Rindfleisch, H. 1975. Non-ribosomal biosynthesis of the cyclic octadecapeptide alamethicin. *Acta Microbiol. Acad. Sci. Hung.*, 22: 411-418.

Kleus, P.F. and Lang, J.F. 1956. Microbiological factors in the preservation of paint. *Chem. Abs.*, 50: 10327d.

Kvasnikov, E.I., Malashenko, Yu. R and Ramanovskaya, V.A. 1971. Effect of ethanethiol on the growth of microorganisms. *Chem. Abs.*, 75: 85634.

Leigh, C. and Taylor, A. 1976. The chemistry of the epipolythiopiperazine-3,6-diones. Advances in chemistry series No. 149, Mycotoxins and other fungal related food problems. Ed. J. V. Rodricks. *Amer. Chem. Soc.*, p. 228-275.

Lew, J.D. and Wilcox, W.W. 1981. The role of selected deuteromycetes in the soft-rot of wood treated with pentachlorophenol. *Chem. Abs.*, 95: 188856.

Lewis, J.A. and Papavizas, G.C. 1984. A new approach to stimulate population proliferation of Trichoderma species and other potential biocontrol fungi introduced into natural soils. *Phytopathology*, 74: 1240-1244.

Liss, S.N., Brewer, D., Taylor, A. and Jones, G.A. 1985. Antibiotic activity of an isocyanide metabolite of Trichoderma hamatum against rumen bacteria. *Can. J. Microbiol.*, 31: 767-772.

Lowe, G., Taylor, A. and Vining, L.C. 1966. Sporidesmins. Part VI. Isolation and structure of dehydrogliotoxin a metabolite of *Penicillium terlikowskii*. *J. Chem. Soc.* (C), 1799-1803.

Madaan, S.L. and Chohan, J.S. 1978. Resident mycoflora on pegs of groundnut as effected by seed and soil treatment with fungicides. *Indian J. Mycol. Plant Pathol.*, 8: 149-152.

Manyu, S.K.K. 1980. The physiologically active substance SC2051. *Chem. Abs.*, 93: 112329.

Marasas, W.F.O., Bamburg, J.R., Smalley, E.B., Strong, F.M., Ragland, W.L. and Degurse, P.E. 1969. Toxic effects on trout, rats and mice of T_2-toxin produced by the fungus *Fusarium trincinctum*. *Toxicol. Appl. Pharmacol.*, 15: 471-82.

Matsumora, F. and Bousch, G.M. 1968. Degradation of insecticides by a soil fungus, Trichoderma viride. *J. Eccon. Entomol.*, 61: 610-612.

Mazur, F.F. 1979. Effect of Trichoderma viride on synthetic rubbers and polyethylene. *Chem. Abs.*, 90: 204954.

Menzel, A.E.O., Wintersteiner, O. and Hoogerheide, J.C. 1944. The isolation of gliotoxin and fumigacin from culture filtrates of Aspergillus fumigatus. *J. Biol. Chem.*, 152: 419-429.

Merlier, O.A.M., Boirie, J.M., Pons, J.B. and Renaud, C.M. 1985. Strain of Trichoderma harzianum, its isolation, its culture, peptides or compounds produced by this strain and application of this strain and these peptides or the product produced by the culture process as a means for biological control in the form of an agricultural fungicide. *Chem. Abs.*, 102: 183747.

Merrill, W., French, D.W. and Hossfield, R.L. 1965. Wood fibreboard studies. II. Effects of common molds on the physical and chemical properties of wood fibreboard. *Tappi*, 48: 470-474.

Meyer, C.E. and Reusser, F. 1967. A polypeptide antibacterial agent isolated from Trichoderma viride. *Experientia*, 23: 85-6.

Miller, P.A., Milstrey, K.P. and Trown, P.W. 1968. Specific inhibition of viral ribonucleic acid replication by gliotoxin. *Science*, 159: 431-2.

Mirocha, C.J. 1983. Developments in Food Science. 4. Trichothecenes chemical, biological and toxicological aspects. Ed. Y. Uneno, Elsevier, Amsterdam, p. 177-194.

Mitchell, C.P. and Dix, N.J. 1975. Growth and germination of Trichoderma spp. under the influence of soil fungistasis. Trans. Brit. Mycol. Soc., 64: 235-41.

Mitzutani, S., Kuwata, M., Hatori, H. and Okada, S. 1980. Storage of chrome leather. Chem. Abs., 92 60360.

Moelhave, L. 1977. The relation between the tree formaldehyde concentration in stored (urea-formaldehyde) chipboard and the formaldehyde concentration in the air. Holzforsch Holzverwert, 29: 73-4.

Moffatt, J.S., Bu'Lock, J.D. and Yuen, T.H. 1969. Viridiol, a steroid-like product from Trichoderma viride. Chem. Commun., 839.

Mohr, H. and Kleinkauf, H. 1978. Alamethicin biosynthesis. Acetylation of the amino terminus and attachment of phenylalaninol. Biochim. Biophys. Acta, 526: 375-386.

Moreau, R. and Augier, J. 1962. The utilization of vanillin by soil microorganisms. Compt. Rend., 254: 555-7.

Moore-Landecker, E. and Stotzky, G. 1972. Inhibition of fungal growth and sporulation by volatile metabolites from bacteria. Can. J. Microbiol., 18: 957-962.

Moss, M.O., Jackson, R.M. and Rogers, D. 1975. The characterization of 6-(pent-1-enyl)-α-pyrone from Trichoderma viride. Phytochemistry, 14: 2706-2708.

Mukasheva, G.M. 1976. Action of hexachlorobutadiene on pure cultures of microscopic fungi. Chem. Abs., 82: 11637.

Müllbacher, A. and Eichner, R.D. 1984. Immunosuppression in vitro by a metabolite of a human pathogenic fungus. Proc. Natl. Acad. Sci. (U.S.A.), 81: 3855-7.

Nagaraj, R. and Balaram, P. 1981a. Solution phase synthesis of alamethicin I. Tetrahedron, 37: 1263-1270.

Nagaraj, R. and Balaram, P. 1981b. Alamethicin, a transmembrane channel. Acc. Chem. Res., 14: 356-62.

Nago, H. and Ishikawa, H. 1970. Anthraquinone pigments and antibiotics formed by Hypocrea austro-grandis. Chem. Abs., 75: 18551.

Nair, M.S.R. and Carey, S.T. 1979. Metabolites of Pyrenomycetes. XI. Polyketides from Hypocreales. Mycologia, 71: 1089-96.

Nair, M.S.R., Carey, S.T. and Ananthasubramanian, L. 1982. Metabolites of pyrenomycetes. XV. Biogenesis of the antitumor antibiotic, (+) R-avellaneol. J. Nat. Prod., 45: 644-5.

Nazarova, E.V. and Zakharova, I. Y. 1982. Isolation and characterization of a Gliocladium zaleskii 11313 phytotoxic substance. Mikrobiol. Zh. (Kiev), 44: 43-48.

Nelson, E.E. 1972. Effect of urea and wood shavings on populations of soil microfungi especially Trichoderma spp. Microbios., 5: 69-72.

Nelson, E.E. 1976. Effect of urea on Poria weirii and soil microbes in an artificial system. Soil Biol. Biochem., 8: 51-53.

Nilsson, T. and Assarsson, A. 1970. Treatment of wood chips with Trichoderma lignorum to descrease resin content. U.S. 3486969; Chem. Abs., 72: 102034.

Nobuhara, M., Tazima, H., Shudo, K., Itai, A., Okamoto, T. and Iitaka, Y. 1976. A fungal metabolite, novel isocyanoepoxide. Chem. Pharm. Bull., 24: 832-834.

Ooka, T. 1977. Physiologically active substance No. 1037. Chem. Abs., 87: 166000.

Ooka, T., Shimojima, Y., Akimoto, T., Takeda, I., Senoh, S. and Abe, J. 1966. A new antibacterial peptide suzukacillin. Agric. Biol. Chem., 30: 700-702.

Ooka, T. and Takeda, I. 1974. The relationship between α-aminoisobutyrate and L-valine for the suzukacillin formation. Agric. Biol. Chem., 38: 19-27.

Pandey, R.C., Cook, J.C. and Rinehart, K.L. 1977. High resolution and field desorption mass spectrometry studies and revised structures of alamethicins I and II. J. Amer. Chem. Soc., 99: 8469-8483.

Parry, R.J. and Hanh Phuoc Buu. 1982. Biosynthesis of an isonitrile acid from Trichoderma hamatum. Tet. Let., 1435-8.

Pashenko, A.A., Vorenkov, M.G., Koval, E.Z., Vlasova, N.N., Shevchenko, L.A. and Sviderskii, V.A. 1978. Study of the resistance of organosilicon protective coatings to molds. Chem. Abs., 89: 192306.

Patil, B.C., Sharma, R.P., Salunke, D.K. and Salunke, K. 1972. Evaluation of solanine toxicity. Chem. Abs., 77: 148228.

Patil, K.C., Matsumura, F. and Boush, G.M. 1970. Degradation of Endrin, Aldrin and DDT by soil microorganisms. Appl. Microbiol., 19: 879-881.

Pitel, D.W., Arsenault, G.P. and Vining, L.C. 1971. Cyclonerodiol, a sesquiterpene metabolite of Gibberella fujikuroi. J. Antibiot., 24: 483-4.

Peeples, J.L. 1972. Effect of the herbicide EPTC (ethyl N,N-dipropylthiocarbamate) on growth responses, antagonism and pathogenesis associated with Sclerotium rolfsii and Trichoderma viride. Chem. Abs., 76: 82068.

Petcher, T.J., Weber, H.P. and Ruegger, A. 1976. Cyrstal and molecular structure of an iodo derivative of the cyclic undecapeptide cyclosporin A. Helv. Chim. Acta, 59: 1480-1488.

Pettersson, G. 1964. Synthesis of 2,3-dihydroxy-5,6-dimethyl-1,4-benzoquinone and its monomethyl ether. Acta Chem. Scand., 18: 2309-2312; idem, 1965, New phenolic metabolites from Gliocladium roseum, ibid. 19: 2303-2308.

Pommer, E.H. 1966. The effect of pyramin on soil fungi. Chem. Abs., 64: 1287f.

Popescu, G. 1979. Protection of corrugated carton wrapping, I. Manufacture of microorganism resistant corrugated cartons. Chem. Abs., 90: 7870.

Pratt, B.H., Sedgley, J.H., Heather, W.A. and **Shepherd, C.J.** 1972. Oospore production in *Phytophthora cinnamomi* in the presence of *Trichoderma koningii. Aus. J. Biol. Sci.,* 25: 861-3.

Reeves, R.J. and **Jackson, R.M.** 1972. Induction of *Phytophthora cinnamomi* oospores in soil by *Trichoderma viride. Trans. Brit. Mycol. Soc.,* 59: 156-159.

Reusser, F. 1966. Biosynthesis of antibiotic U-22324 cyclic polypeptide. *J. Biol. Chem.,* 242: 243-7.

Rifai, M.A. 1969. A revision of the genus *Trichoderma. Mycol. Papers* 116: 1-56.

Rightsel, W.A., Schneider, H.G., Sloan, B.J., Graf, P.R., Miller, F.A., Bartz, G.R., Ehrlich, J. and **Dixon, E.J.** 1964. The antiviral activity of gliotoxin and gliotoxin acetate. *Nature (Lond.). 204:* 1333-4.

Rüegger, A., Kuhn, M., Lichti, H., Loosli, H., Huguenin, R., Quiquerez, C. and **von Wartburg, A.** 1976. Cyclosporin A ein immunsuppressiv wirksamer Peptidmetabolit aus *Trichoderma polysporum* (Link ex Pers.) Rifai. *Helv. Chim. Acta,* 59: 1075-1092.

Ryu, D.D.Y. and **Mandels, M.** 1980. Cellulases: biosynthesis and applications. *Enzyme Microb. Technol.,* 2: 91-102.

Saccardo, P.A. 1883. Sylloge fungorum, 2: 469, 527, 529, 536.

Saito, M., Yamanishi, T. and **Tsuruta, O.** 1981. Studies on the odor substances of fungi. Part I. Identification of the fungal odors produced on the synthetic medium. *Chem. Abs.,* 94: 79943.

Sakaguchi, K., Kurani, R. and **Murata, M.** 1976. Assimilation of formaldehyde and other C_1 compounds by *Gliocladium deliquescens* and *Paecilomyces varioti. Chem. Abs.,* 85: 2305.

Sakata, K., Masago, H., Sakurai, A. and **Takahashi, N.** 1982. Isolation of aspirochlorine (= antibiotic A30641) possessing a novel dithioketopiperazine structure from *Aspergillis flavus. Tet. Let.,* 2095-8.

Sax, N.I. 1968. Dangerous properties of industrial materials. 3rd ed. Van Nostrand Reinhold, New York, p. 1071.

Schappert, K.T. and **Khachatourians, G.E.** 1983. Effects of fusariotoxin T_2 on *Saccharomyces cerevisiae* and *Saccharomyces carlsbergensis. Appl. Environ. Microbiol.,* 45: 862-7.

Schmitt, H. and **Jung, G.** 1985. Total synthesis of the α-helical eicosapeptide antibiotic alamethicin. *Liebigs Ann. Chem.,* 321-344.

Selivokhin, P.I., Bolonina, E.I. and **Zemlyanskii, N.N.** 1974. Organotin compounds as antiseptics for film materials. *Chem. Abs.,* 80: 56063.

Senior, E., Bull, A.T. and **Slater, J.H.** 1976. Enzyme evolution in a microbial community growing on the herbicide dalapon. *Nature* (Lond.). 263: 476-9.

Shaw, I.M. and **Taylor, A.** 1986. The chemistry of peptides related to metabolites of *Trichoderma* spp. 2. An improved method of characterization of peptides of 2-methylalanine. *Can. J. Chem.,* 64: 164-173.

Shteinberg, B.I., Trakhtenberg, S.I., Datsyuk, N.M., Kovalyuk, E.K., Gura, I.S. and **Shakh, E.S.** 1983. Biological stability of poly(vinyl alcohol)-based polymers. *Mikrobiol. Zh.* (Kiev), 45: 20-24.

Sierota, Z.H. 1977. Yield of dry mycelium of *Trichoderma viride* Pers. ex Fr. on some carbon and nitrogen sources. *Eur. J. For. Pathol.,* 7: 65-76.

Singh, R., Iyenga, L. and **Rao, A.V.S.P.** 1977. Effect of insecticides on fungal enzymes. *J. Gen. Appl. Microbiol.,* 23: 119-26.

Slater, G.P., Haskins, R.H., Hagge, L.R. and **Nesbitt, L.R.** 1967. Metabolic products from a *Trichoderma viride* Pers. ex. Fries. *Can. J. Chem.,* 45: 92-96.

Sokoloff, B. and **Toda, Y.** 1967. Antiviral antibiotic from *Trichoderma todica* and its production method. *Chem. Abs.,* 67: 62990.

Spencer, H.C., Rowe, V.K. and **McCollister, D.D.** 1950. Dehydroacetic acid. I. Acute and chronic toxicity. *J. Pharamacol. Explt. Therap.,* 99: 57-68.

Stipanovic, R.D. and **Howell, C.R.** 1982. The structure of gliovirin, a new antibiotic from *Gliocladium virens. J. Antibiotics,* 35: 1326.

Stipanovic, R.D. and **Howell, C.R.** 1983. The X-ray crystal structure determination and biosynthesis studies of the antibiotic heptelidic acid. *Tetrahedron,* 39: 1103-7.

Stranks, D.W. 1971. Trichoderma viride enzymic degradation of wood structure. *Chem. Abs.,* 74: 23734.

Stratton, G.W. 1983. Interaction effects of permethrin and atrazine combinations towards several non-target microorganisms. *Bull. Eniron. Contam. Toxicol.,* 31: 297-303.

Suess, A. and **Netzsch-Lehner, A.** 1969. Effect of various micro-organisms on the intensity of decomposition of diesel oil. *Z. Pflanzenernaehr. Bodenk.,* 123: 232-9.

Sukhorukova, Z.A. 1972. Antibiotic properties of fungi isolated from the rhizosphere of barley and oats. *Mikrobiol. Zh.* (Kiev), 34: 602-5.

Tabata, T. and **Kondo, T.** 1977. Protection of Shiitake fungus from mycoparasites by fungicidal agents. 4. Selective antifungal activity of 5-substituted methyl 2-benzimidazole carbamates, 2-aryl- and 2-alkyl-substituted benzimidazole derivatives upon the mycelium of Shiitake fungus and its mycoparasites. *Mokuzai Gakkaishi* 1977, 23: 504-508; *Chem. Abs.,* 88: 33004.

Tamimi, K.M. and **Hutchinson, S.A.** 1975. Differences between the biological effects of culture gases from species of *Trichoderma. Trans. Brit. Mycol. Soc.,* 64: 455-463.

Tamura, A., Kotani, H. and **Naruto, S.** 1975. Trichoviridin and dermadin from *Trichoderma* sp. TK-1. *J. Antibiotics,* 28: 161-162.

Taylor, A. 1970. The occurrence, chemistry, and toxicology of the microbial peptide-lactones. *Ad. Appl. Microbiol.* 12: 189-276.

Taylor, A. 1971. The toxicology of sporidesmins and other epipolythiadioxpiperazines. In Microbial Toxins. Vol. 7, Ed. S. Kasis, A. Ciegler and S. J. Ajl. Academic Press, New York, p. 363.

Thomson, A.W., Whiting, P.H. and Simpson, J.G. 1984. Cyclosporine: immunology, toxicity and pharmacology in experimental animals. *Agents Actions*, 15: 306-27.

Traber, R., Kuhn, M., Loosli, H., Pache, W. and **von Wartburg, A.** 1977. Neue Cyclopeptide aus *Trichoderma polysporum* (Link ex Pers.) Rifai: die Cyclosporine B, D, und E. *Helv. Chim. Acta*, 60: 1568-1578.

Traber, R., Loosli, H., Hofmann, H., Kuhn, M. and **von Wartburg, A.** 1982. Isolierung und Strukturermittlung der neuen Cyclosporine E, F, G, H und I. *Helv. Chim. Acta*, 65: 1655-1677.

Tripathi, R.D., Tripathi, S.C. and **Dixit, S.N.** 1980. Structure activity relationship among some fungitoxic α-napthoquinones of angiosperm origin. *Ag. Biol. Chem.*, 44: 2483-5.

Ueno, Y. 1983. Developments in Food Science. 4. Trichothecenes, chemical, biological and toxicological aspects. Ed. Y. Ueno, Elsevier, Amsterdam, p. 135-146.

Ueno, Y., Nakajima, M., Sakai, K., Ishii, K., Sato, N. and **Shimada, N.** 1973. Comparative toxicology of trichothec mycotoxins: inhibition of protein synthesis in animal cells. *J. Biochem.*, 74: 285-296.

Upjohn Company. 1969. The antibiotic alamethicin. U. K. Patent 1152659.

Usui, M. and **Iida, S.** 1980. Control of pathogenic fungi in the nursery cases of rice young seedlings by chemicals. *Chem. Abs.*, 92: 1505.

Veldre, I., Karpunin, B.I. and **Maasik, I.** 1971. Toxicological characteristics of 5-methylresorcinol. *Chem. Abs.*, 74: 51746.

Verrall, A.F. 1949. Some molds under wood favored by certain toxicants. *J. Agr. Res.*, 78: 695-703.

Vischer, E.B. 1953. The structures of aurantio- and rubro-gliocladin and glioresein. *J. Chem. Soc.*, 815-820.

Wakazawa, T., Niwa, T. and **Ichinose, K.** 1965. Degradation of wood pulp and cotton linters by *Trichoderma koningii* cellulase. *Chem. Abs.*, 62: 16500 h.

Webster, J. and **Lomas, N.** 1964. Does *Trichoderma viride* produce gliotoxin and viridin? *Trans. Brit. Mycol. Soc.*, 47: 535-540.

Weil, C. 1984. Cyclosporin A; review of results in organ and bone marrow transplantation in man. *Med. Res. Rev.*, 4: 221-65.

Weindling, R. 1932. *Trichoderma lignorum* as a parasite of other soil fungi. *Phytopathology*, 22: 837-845.

Weindling, R. 1934. Studies in a lethal principle effect in the parasitic association of *Trichoderma lignorum* on *Rhizoctonia solani* and other soil fungi. *Phytopathology*, 24: 1153-1179.

Wenger, R.M. 1984. Synthesis of cyclosporin. Total synthesis of cyclosporin A and cyclosporin H, two fungal metabolites isolated from the species *Tolypocladium inflatum* Gams. *Helv. Chim. Acta*, 67: 502-525.

Widden, P. and **Abitol, J.J.** 1980. Seasonality of *Trichoderma* species in a spruce-forest soil. *Mycologia*, 72: 775-784.

Whitman, W.B. and **Wolfe, R.S.** 1980. Presence of nickel in factor F_{430} from *Methanobacterium bryantii*. *Biochem. Biophys. Res. Commun.*, 92: 1196-1201.

Yamamoto, I., Hemmi, T. and **Yamano, T.** 1970. Sesquiterpenoid antibiotics from molds. *Chem. Abs.*, 72: 76058.

Yamamoto, Y., Nitta, K., Oohata, Y. and **Furukawa, T.** 1972. Studies on the metabolic products of a strain of *Aspergillus fumigatus* DH413. V. A new metabolite produced by ethionine inhibition. *Chem. Pharm. Bull.*, 20: 931-5.

Yamano, K. 1979. Observations of fungal attacks on PVC. *Chem. Abs.*, 91: 124303.

Yoshimoto, T., Samejima, M., Kimura, T., Yoshitomi, K. and **Nakanishi, K.** 1984. Growth inhibitors of Trichoderma sp. in hot-water extractives from barks of *Quercus* sp. *Chem. Abs.*, 100: 188827.

Zayed, S.H.A.D., Mostafa, I.Y., Farghaly, M.M., Attaby, H.S.H. and **Adam, Y.M.** 1982. Degradation of trifluorin by *Trichoderma viride*. *Chem. Abs.*, 97: 174771.

Zoltanska, E. 1984. Effect of some fungicides on selected soil fungi. *Chem. Abs.*, 101: 145899.