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HERBICIDE SELECTIVITY

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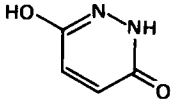
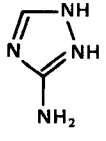
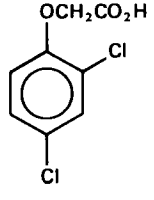
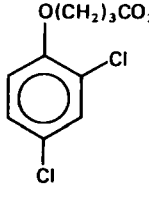
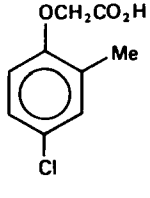
I. INTRODUCTION

This paper is not purely a review in the generally accepted sense, but rather a discussion paper in which the biological basis of herbicide selectivity is explored. The definition of selectivity as the practice of injuring one or more living species without harming the other species with which the first is (are) in intimate contact is cardinal to these considerations. Remarkable herbicide selectivity is shown by some of the agents mentioned in this narrative (see Table 1*), which kill both the grasses and the broad leaved weeds in a particular ecosystem, but which spare the crop-plant seedlings.

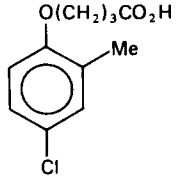
Traditionally, the penetration, uptake, translocation and metabolism of herbicides in plants are always regarded as the fundamental currency of selectivity. As a general rule these parameters are accepted, but a problem occurs as one of them, namely herbicide metabolism in plants, is considered to be more important than the other ones. The present article accordingly lays stress on differences in the activity of specific enzymes in various plant species, and the greatly expanded data that are now available enable a fuller interpretation of herbicide metabolism and the accompanying bioactivation or

* Both in Table 1 and throughout the text of this article, the crop plants are referred to by their common English names and the weed species by their Latin names. In Table 1, pre-em, etc. refer to pre-emergence, etc.

Table 1. Herbicidal selectivity

Trivial name	Structure	Uses
Acylhydrazides		
Maleic hydrazide		Used to retard the growth of grass and hedges, to inhibit the sprouting of beets and potatoes, and to prevent sucker development in tobacco.
Daminozide Succinic acid	$Me_2NNCCH_2CH_2CO_2H$ (H, O) mono-(2,2-dimethylhydrazide)	Employed to improve fruit quality, and to reduce vegetative growth of groundnuts.
Aminotriazole Amitrole 3-amino-1H,1,2,4-triazole		Non-selective herbicide used in apple and pear orchards, etc.
Aryloxyalkanoic acids		
2,4-D (2,4-dichlorophenoxy)acetic acid		For weed control in cereal crops (Nutman, Thornton & Quastel, 1945; Slade, Templeman & Sexton, 1945).
2,4-DB		Used on lucerne, undersown cereals and grassland.
4-(2,4-dichlorophenoxy)butyric acid		
MCPA		Control of annual and perennial weeds in cereals, grassland and turf (Nutman, Thornton & Quastel, 1945; Slade, Templeman & Sexton, 1945).
4-chloro-*o*-tolyloxyacetic acid		

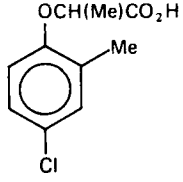
MCPB



4-(4-chloro-*o*-tolyloxy)butyric acid

For control of annual and perennial weeds in undersown cereals, peas and grassland (Wain & Wightman, 1954).

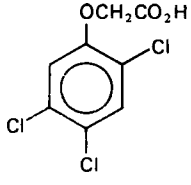
MCPP



(±)-2-(4-chloro-*o*-tolyloxy)propionic acid

For control of *Stellaria media* and *Galium aparine* and other weeds in cereals (Fawcett *et al.*, 1953).

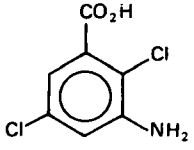
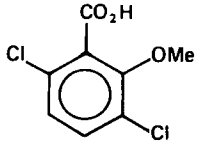
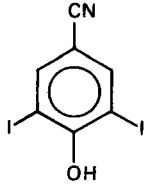
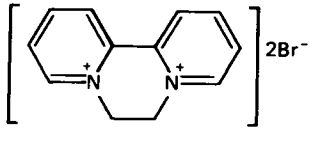
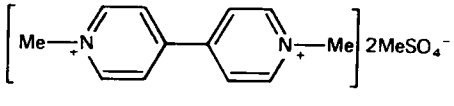
2,4,5-T



(2,4,5-trichlorophenoxy)acetic acid

Used with 2,4-D for control of shrubs and trees (Hamner & Tukey, 1944).

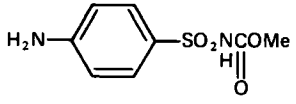
Table 1 (*cont.*)

Trivial name	Structure	Uses
Benzoic acids and derivatives		
Chloramben 3-amino-2,5-dichlorobenzoic acid		Used before planting and pre-em, for control of grasses and broad-leaved weeds in seedling asparagus, groundnuts, maize, navy beans soya-beans, squash, sunflower, etc.
Dicamba 3,6-dichloro-*o*-anistic acid		Used in combination to control broad leaved annual and perennial weeds, *Convolvulus arvensis*, *Galium aparine*, *Polygonum persicaria*, etc. in cereals.
Ioxynil 4-hydroxy 3,5-di-iodobenzo-nitrile		Contact herbicide used on broad-leaved weeds in cereals, onions, newly sown turf and sugar-cane (Carpenter & Heywood, 1963; Wain, 1963; Hart, Bishop & Cooke, 1964).
Bipyridinium salts		
Diquat 1,1′-ethylene-2,2′-bipyridinium dibromide		Used for aquatic weed control, potato-haulm destruction and seed-crop destruction (Brian *et al.*, 1958).
Paraquat 1,1′-dimethyl-4,4′-dipyridinium methosulphate		A contact herbicide, used for cleaning stubble, pasture renovation, the desiccation of various crops and the weed control of plantation crops (Brian *et al.*, 1958).

Carbanilates and Acylanilides

Asulam

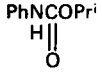
methyl sulphanilylcarbamate



Used to control *Rumex* spp. in pasture and decidous fruit orchards, grasses in tropical tree crops, *Pteridium aquilinium* in pastures and forestery, *Avena fatua* in linseed, etc.

Propham

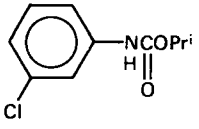
Isopropylcarbanilate



Used to control annual grass weeds in peas, and sugar-beet or as a combination herbicide for fodder crops, lettuce, etc. (Templeman & Sexton, 1945).

Chlorpropham

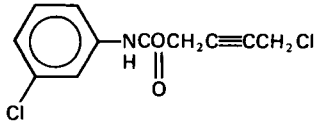
Isopropyl 3-chlorocarbanilate



Alone or with other herbicides to control *Stellaria media* and germinating weed in carrots, leeks, lettuce, onions, etc. Used to inhibit sprouting of ware potatoes (Witman & Newton, 1951).

Barban

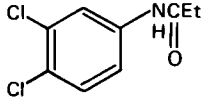
4-chlorobut-2-ynyl-3-chloro-carbanilate



For control of *Avena fatua* in barley, wheat, broad beans, lucerne, rape, soyabeans, sunflower, etc. (Crafts, 1964).

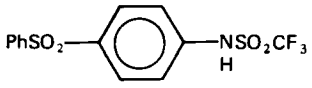
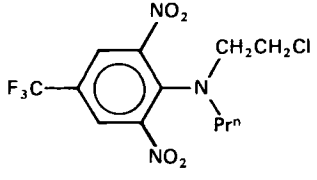
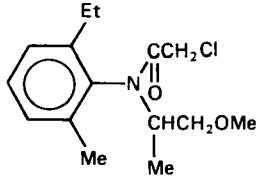
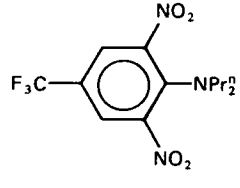
Propanil

3′,4′-dichloropropionanilide



Used post-em, for control of *Echinochloa crus-galli* in rice (Smith, 1961).

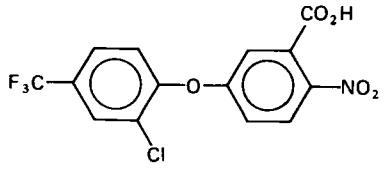
Table 1 (*cont.*)

Trivial name	Structure	Uses
Perfluidone 1,1,1-trifluoro-4′-(phenylsulphony)-methanesulphono-*o*-toluidide		Used for control of *Cyperus esculentus* and many grass and broad-leaved weeds in cotton, tobacco, etc.
Chlorinated aliphatic acids		
Dalapon 2,2-dichloropropionic acid	$MeCCl_2CO_2H$	Used to control annual and perennial grasses on non-crop areas and for crops like cotton.
Dinitroanilines and surrogates		
Fluchloralin *N*-(2-chloroethyl)-α,α,α-trifluoro-2,6-dinitro-*N*-propyl-*p*-toluidine		Pre-plant or pre-em, herbicide against grasses and broad-leaved weeds. Used for cotton, groundnuts, jute, potatoes, rice, soyabeans and sunflowers.
Metolachlor 2 chloro-6′-ethyl-*N*-(2-methoxy-1-methylethyl)acet-*o*-toluidide		Effective mainly on grasses. Used selectively in cotton, groundnuts, maize, potatoes, sorghum, sugar-beet, sugar-cane, sunflowers, and other broad-leaved crops.
Trifluralin α,α,α-trifluoro-2,6-dinitro-*N*,*N*-dipropyl-*p*-toluidine		Pre-em. herbicide against annual grasses and broad-leaved weeds. Effective for beans, brassicas, cotton, groundnuts, forage, legumes, soyabeans, sugar-beet, sunflowers, etc. (Probst *et al.*, 1967).

Diphenyl ethers

Acifluorfen

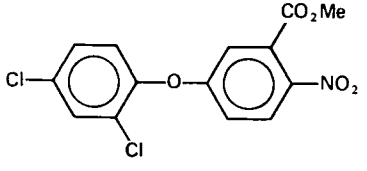
5-(2-chloro-α,α,α-trifluoro-*p*-tolyloxy)2-nitro-benzoic acid



Selective post-em. herbicide against broad-leaved weeds in groundnuts, rice, soyabeans and wheat.

Bifenox

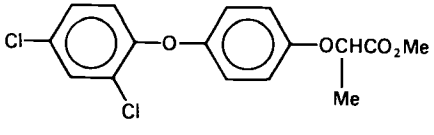
Methyl 5-(2,4-dichlorophenoxy)-2-



Used for pre-em, control of broad-leaved weeds and some grasses in cereals, maize, rice, sorghum and soyabeans.

Diclofop-methyl

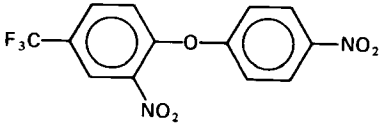
Methyl (RS)-2-[4-(2,4-dichloro-phenoxy)phenoxy]propionate



Used for post-em. control of *Avena fatua*, *A. ludoviciana*, *Echinochloa crus-galli*, *Eleusine indica Setaria faberi*, *S. lutescens*, *S. irridis*, *Panicum dichotamiflorum*, *Lolium multiflorum*, *Leptochloa* spp., etc. in beans, cereals, carrots, clover, cucumbers, groundnuts, lucerne, potatoes, rape, soyabeans, sugar-beet, etc. (Shimabukuro *et al.*, 1978).

Fluorodifen

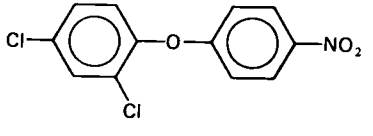
4-nitrophenyl-α,α,α-trifluoro-2-nitro-*p*-tolylether



Pre- and post-em. contact herbicide, used for drilled rice.

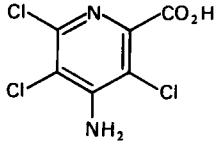
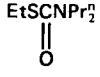
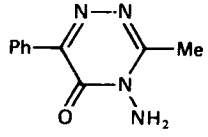
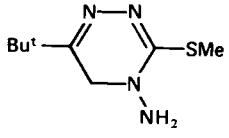
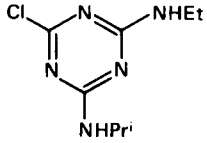
Nitrofen

2,4-dichlorophenyl *p*-nitrophenylether



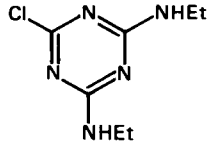
Used for weed control in cereals pre-em.

Table 1 (*cont.*)

Trivial name	Structure	Uses
Picloram 4-amino-3,5,6-trichloropicolinic acid		Used alone or in combination with 2,4-D against deeply rooted perennials on non-crop land (Hamaker *et al.*, 1963).
Thiocarbamates EPTC *S*-ethyl-*N*,*N*-dipropylthiocarbamate		Useful for control of *Agropyron repens* and perennial *Cyperus* spp.
asym-Triazinones Metamitron 4-amino-3-methyl-6-phenyl-1,2,4-triazin-5(4H)-one		Used for high selectivity in sugar- and fodder-beet crops.
Metribuzin 4-amino-6-t-butyl-3-methylthio-1,2,4-triazin-5(4H)-one		Used pre- and post-em. to control weeds in asparagus, lucerne, potatoes, soyabeans, sugar-beet, tomatoes, etc.
sym-Traizines Atrazine 2-chloro-4-ethylamino-6-isopropylamino *sym*-triazine		Used as selective herbicide in asparagus, grass crops, maize, pineapple, sorghum and sugar-cane.

Simazine

2-chloro-4,6-*bis*(ethylamino)-*sym*-triazine

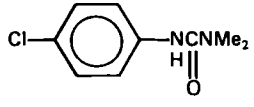


Pre-em. herbicide for control of broad-leaved and grass weeds in crops like asparagus, berry crops, citrus, cocoa, coffee, hevea, hops, olives, orchards, sisal, sugar-cane, tea, vineyards, etc. A major use is on maize (Gast, Knüsli & Gysin, 1956).

Ureas

Monuron

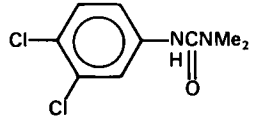
3-(p-chlorophenyl)-1,1-dimethylurea



Used for total weed control (Bucha & Todd, 1951).

Diuron

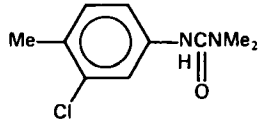
N'-(3,4-dichlorophenyl)-*N*,*N*-dimethylurea



For general weed control on non-crop areas, as well as pre-em. selectivity on asparagus, citrus, cotton, pineapple and sugar-cane (Bucha & Todd, 1951).

Chlortoluron

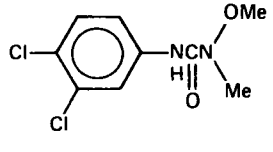
3-(3-chloro-*p*-tolyl)-1,1-dimethylurea



Used as soil-acting herbicide in cereal crops against *Avena fatua* and *Alopecurus mysosuroides* (Richardson & Parker, 1978).

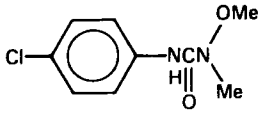
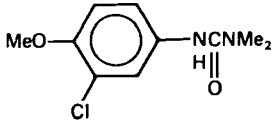
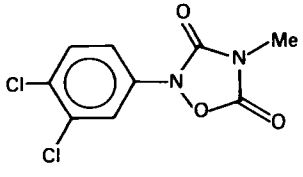
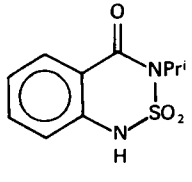
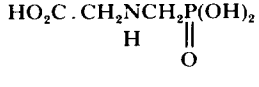
Linuron

3-(3,4-dichlorophenyl)-1-methoxy-1-methylurea



Used in asparagus, cotton, maize, potatoes and soyabeans pre-em.

Table 1 (*cont.*)

Trivial name	Structure	Uses
Monolinuron 3-(4-chlorophenyl)-1-methoxy-1-methylurea		Used in asparagus, beans, maize and potatoes pre-em.
Metoxuron 3-(3-chloro-4-methoxyphenyl)-1,1-dimethylurea		Used in carrots and cereals against *Alopecurus mysosuroides*, *Aperca spica-venti*, *Avena fatua* *Lolium remotum*, and *Phalaris canariensis* (Richardson & Parker, 1978).
Methazole 2-(3,4-dichlorophenyl)-4-methyl-1,2,4-oxadiazolidine		Selective herbicide against grasses and many broad-leaved weeds, and used pre-em. in potatoes and garlic; also as a directed spray on to weeds in citrus, nuts, stone fruits, tea and vines.
Miscellaneous Bentazone 3-isopropyl-(1H)-2,1,3-benzo-thiadiazin-4(3H)-one-2,2-dioxide		Contact herbicide for control of *Anthemis* and *Matricaria* spp., *Chrysanthemum segetum*, *Galium aparine*, *Lapsana communis* and *Stellaria media* in cereals; also in maize, rice and soyabeans.
Glyphosate *N*-(phosphonomethyl)glycine		Non-selective herbicide, which is very effective against deep-rooted, perennial spp.

detoxification to be made than was previously possible. In fact, if the disturbance in plant biochemistry by herbicides is as important as it would appear to be, then

(i) exposure of plants to relevant foreign compounds would be expected to stimulate the mixed-function oxidases concerned with herbicide metabolism;

(ii) various crop-plant cultivators and weed biotypes might be expected to show differential tolerance to a specific herbicide; and

(iii) appropriate genetic manipulation would be expected to improve the resistance of particular crop plants to specific herbicides, as the enzymes are themselves products of the cellular genes (Haldane, 1920, 1954).

Conversely, it follows (iv) that differences in activity of the constitutive enzymes between plants may assist in the modelling of new herbicides.

In view of the upsurge of interest in molecular genetics and as the new techniques that have been developed in the last few years have now been applied successfully to plant cells, it is particularly timely to review concepts (ii), (iii), which have a genetic connotation. Sub-sections III. 4 and 5 present the available evidence.

A second issue arises out of the omission of contingent material from earlier accounts of herbicide selectivity and, for example, the reciprocal influence of higher plant allelopathy appears to be relevant. The word Allelopathie (allelopathy) was coined by Molisch (1937) to denote biochemical interactions between different plant species, due to the chemicals which they release into the environment, and he had already compiled a considerable body of information on this subject before research on commercial herbicides began. Accordingly, up-to-date evidence is now presented for the idea of using allelopathic principles from various sources as replacement herbicides.

A third problem concerns the small number of herbicides that do not appear to conform with the principles of selectivity that have emerged. It seems (i) that the modest degree of selectivity, which some of these show, cannot be reckoned in terms of the usual currency (*q.v.*), and (ii) that the remainder are simply unselective.

II. DIFFERENTIAL PENETRATION, UPTAKE AND TRANSLOCATION

(1) *Selective uptake from the soil*

At first sight, the different morphology, physical properties and rate of development of the plant–root system would be considered likely to affect the rate of uptake of soil-applied herbicides into various living species, and in some cases, the efficacy of herbicides has been found to parallel the differential root absorption of various species. The germinating weeds in these circumstances were killed just before or soon after their emergence through the surface of the ground. Thus, in the case of diclofop-methyl, the root absorption of *Avena fatua* (susceptible) was found (Nojavan & Evans, 1980) to be greater than that of barley (resistant), but both the translocation and the distribution of this herbicide in the two species were similar. Clearly, those systemic herbicides, which are absorbed through the roots, are translocated upwards by the phloem (i.e. symplastically) to the growing points of the young plants, where they exert their effects. It is sometimes possible to impose mechanical selectivity on an arable ecosystem by application of soil-acting herbicide when the crop-plant foliage has been established, provided that it is impermeable to a toxic dose of herbicide and a similar result has been obtained by means of directed sprays (Wilson & Burnside, 1973) and granular

formulations. The depth of sowing would also appear to be relevant to mechanical selectivity and, under favourable circumstances, *sym*-triazines may be used for weed control (*Phalaris* ssp.) in wheat seedlings (Eshel, 1972) and pyrazone in sugar-beet (Eshel & Sompolinsky, 1970) (cf. Hauser, Ripper & Scott, 1957; Samples & Parham, 1969).

(2) *Selective penetration into leaves and shoots*

Prime facie evidence suggests that the ease of penetration of some aryloxyalkanoic acids into *Brassica sinapis* and other broad leaved weeds, compared with cereal plants, depends on differences in the morphology and wettability of the leaf surfaces (Hartley, 1960; Holloway, 1970). The herbicides considered in this sub-section are translocated downwards by the xylem (i.e. apoplastically) into the transpiration stream and upward movement appears to depend on the rate of transpiration. Most chemicals reach the living protoplasts (i.e. the symplast) of the mature leaves from which redistribution is limited, but foliarly administered systemic herbicides are transported to the roots. Complication arises where herbicides are absorbed both by the leaves and by the roots (Brian, 1966).

Much of the investigation of herbicide penetration was made with leaf discs in vitro. These workers (Sargent & Blackman, 1969, 1970, 1972; Sargent, Powell & Blackman, 1969; cf. Bukovac *et al.*, 1971) recognized an early stage in leaf development, where the cuticle limits the rate of entry, which seemed to be facilitated by ATP-energized active transport (Sargent & Blackman, 1969, 1970). Whilst this stage may be common to all species, many of them pass through it before the leaves emerge from the buds, whereas in other ones, for example, those of the haricot bean plant, it may be transient but physiologically important and, in still others, it may continue to operate throughout leaf development and growth. The presence of numerous barriers to penetration makes it difficult to assess the role of penetration in herbicide selectivity, and the work of Sargent and Blackman (*q.v.*) did not afford a complete explanation. In other work, some of which involved observations in vivo, a low rate of foliar entry corresponded to resistance to the herbicide concerned. Thus, differences in the rate of ioxynil uptake into barley-, mustard- and pea-plant leaves may contribute to selectivity (Davies *et al.*, 1968). After topical application, more barban was retained by the leaf tips of *Avena fatua* than by those of resistant wheat plants (Neidermyer & Nalewaja, 1970) and eight times as much chloroxuron was found in the leaves of the susceptible annual *Convolvulus tricolor* than in those of resistant soyabean plants (Feeny & Colby, 1968). Foliar absorption of diclofopmethyl was greater in *A. fatua* than in barley, where the translocation and distribution were similar in both species (Nojavan & Evans, 1980). Resistance of the field bean to MCPB was attributed partly to the failure of MCPB to penetrate the cuticle as readily as MCPA to which the field bean is susceptible (Kirkwood, Robertson & Smith, 1965, 1968; Kirkwood *et al.*, 1972), and the resistance of barley to picloram was ascribed partly to the slow rate of herbicide uptake (Sharma & Vanden Born, 1973).

(3) *Observations on translocation*

The movement of herbicides away from the site of entry is also potentially important to selectivity. Thus, the symplastic transport of dicamba in *Fagopyrum esculentum* compared with its apoplastic movement in wheat, in which it is metabolized more rapidly, contributes to herbicide selectivity (Quimby & Nalewaja, 1971). A pattern of

absorption/retention by the phloem and of marked downward movement was found for the trunks of susceptible trees painted with 2,4,5-T, whereas in resistant tropical trees the movement was upwards into the transpiration stream (Sandaram, 1965). A complication arises as many compounds, translocated by the phloem, leak into the xylem and are circulated in the plant. Thus, in *Agropyron repens*, dalapon is translocated by the phloem, but leaks into the xylem and very little reaches the roots of topically treated plants (Sagar, 1960). Where drops of 2,4-D were applied to the leaves of haricot bean plants (susceptible) and of sugar-cane (resistant), equal amounts of herbicide had been absorbed by both species after 7 days (Ashton, 1958). Of the observed material 94% was retained by the leaves of sugar-cane compared with 23% in those of haricot beans. A greater 2,4-D concentration was found in the shoots of the haricot bean plants, particularly at the growing points, compared with those of the sugar-cane. The rate of translocation of a particular herbicide, however, is not necessarily commensurate with that of transpiration and O'Brien (1968) found that, although the rate of foliar absorption of 2,4-D by *Avena fatua* is twice that of haricot bean plants, herbicide is retained by the treated leaves of *Avena* but translocated freely in haricot bean plants, despite the fact that the treated leaves of both species were simultaneously exporting nutrients. MCPA and MCPB were absorbed and translocated extensively by *Chenopodium album* (susceptible), but in *Polygonum convolvulus* (resistant), the compounds were retained in the leaves to which they had been applied (Kirkwood, Robertson & Smith, 1965). The penetration of asulam into flax (tolerant) was much more rapid than into *Avena fatua* (susceptible), but herbicide was distributed throughout *A. fatua* seedlings, whereas translocation in flax was very limited, because of contact injury to the leaves (Sharma, Vanden Born & McBeath, 1978). After foliar treatment, the translocation of buthidazole occurred only towards the tip of the treated leaves in maize, whereas in *Amaranthus retroflexus* the herbicide moved acropetally and basipetally (Hatzios & Penner, 1980). Thus, buthidazole, supplied to the roots, reached the shoots of the weed species faster than in maize (Hatzios & Penner, 1980). The foregoing examples show how translocation may contribute to the pattern of herbicide selectivity, but other examples that may have been selected would have appeared less conclusive.

(4) *Concluding remarks*

The weight of evidence in sub-sections II. 1–3 appears to suggest that in addition to herbicide penetration, uptake and translocation another factor, namely herbicide metabolism contributes to selectivity, and an analysis of the interrelation of factors supports this supposition. Thus, a linear model might be constructed in which two outer compartment, representing respectively the uptake and metabolism of foreign compounds in a plant, are coupled through intermediate ones concerned with the elements of transport. No more of a compound would be able to pass any link in this chain than had reached the previous one.

Where the herbicide is unmetabolized both in resistant and in susceptible plants, as in the case of asulam in flax and *Avena fatua*, the model indicates the importance of species differences in uptake and translocation to selectivity, and this was found in practice (Sharma *et al.*, 1978). Again, where the rates of herbicide uptake and metabolism in both resistant and susceptible species are comparable, as in the case in which methazole was administered before emergence to *Matricaria matricaroides*,

Stellaria media and *Veronica persica*, the model infers that species differences in translocation would account for the variation in herbicide concentration in the shoots and for the response of the seedlings. In fact, the smallest proportion of the methazole absorbed was translocated to the shoots in *Veronica*, which was the most tolerant species (Verity, Walker & Drennan, 1981). These examples concern the evidence presented in sub-sections 11. 1-3, but in addition the model emphasizes that a slow rate of herbicide uptake and a rapid rate of metabolism/detoxification are commensurate with species resistance to phytotoxicity. For example (Mueller, Kang & Maruska, 1984), less chlorsulfuron was absorbed and translocated to the shoots of tolerant barley and wheat plants than to these of the susceptible sugarbeet and *Matricaria chamomilla* or to the intermediately susceptible *Viola tricolor*, and the metabolism of this herbicide into inactive polar substances was faster in the roots and shoots of the tolerant species than in those of the more susceptible ones. Clearly, the model also implies that a herbicide with a high rate of uptake would be tolerated provided that there is a matching rate of detoxification. This evidence infers how herbicide metabolism and detoxification disposes of the absorbed phytotoxic material and contributes to the resulting selectivity between species.

III. DEPENDENCE OF SELECTIVITY UPON SPECIES DIFFERENCES IN METABOLISM

Besides profoundly disturbing plant biochemistry by their mode of action, herbicides are themselves metabolized by it with accompanying bioactivation or detoxification. Species show considerable differences in their capacity to transform herbicides and in many cases, the difference in response between susceptible and resistant species parallels a significant difference in metabolic activity. The biochemical mechanisms concerned (Baldwin, 1977) are very similar to those, which have been established in animal tissues (Gillette, 1963), including oxidation leading to the hydroxylation of aromatic compounds and that of aliphatic chains, to oxidative deamination, *N*-alkylation and *O*-dealkylation, to *N*-oxidation and to sulphoxidation, the hydrolysis of esters and amides and the conjugation by glycosidation and reaction with cysteinyl peptides.

(1) *Bioactivation of progenitors*

In the case where the herbicide itself is the progenitor of the active principle, a high activity of the enzymes concerned with bioactivation would seem to be essential to phytotoxicity in susceptible species.

Thus, over fifty years ago, 2-(1-naphthyl)acetonitrile was found to have a growth activity closely resembling that of 2-(1-naphthyl)acetic acid, and this activity was attributed to its biotransformation into the parent acid (Zimmerman & Wilcoxon, 1935). More recently, nitrile hydrolysis has been studied in plants and it was found that, if oat tissues were incubated in 2-(3-indolyl)acetonitrile solution, 2-(3-indolyl)acetic acid was formed in quantity sufficient to be detectable chemically (Stowe & Thimann, 1954), whereas this is not possible with pea-plant tissues (Fawcett, Wain & Wightman, 1960). This evidence strongly suggests that, as the growth of oat and wheat tissues is stimulated by 2-(3-indolyl)acetonitrile, whereas that of pea tissues is not, 2-(3-indolyl)acetonitrile is not an auxin *per se*, but must be transformed into the auxin, 2-(3-indolyl)acetic acid for the ensuing growth to occur. Subsequent isolation of indolylacetonitrilase from the leaves and stem of barley plants (Thimann & Mahadevan,

1958) inferred direct hydrolysis of the nitrile into free carboxylic acid without amide formation. In fact, in wheat, the growth response from the treatment with 2-(3-indolyl)acetamide was less than that with the related acetonitrile (Fawcett *et al.*, 1960).

Some bipyridinium salts, such as diquat, have contact herbicidal properties. Members of this series show a correlation between redox potential and phytotoxicity, and they are activated by a reduction process in the green tissues (Homer, Mees & Tomlinson, 1960). The simultaneous application of monuron, a specific inhibitor of reduction by chloroplasts, delays the onset of the diquat symptoms in light, and bipyridinium compounds have been found to be reduced by illuminated chloroplasts (Good & Hill, 1955). It is probable, therefore, that photochemical processes are involved in the activation of diquat by reduction, but since diquat is also slightly active in the dark, metabolic reduction plays some role (Mees, 1960).

The inactive plant-growth regulators, 2,4-DB and MCPB generate the active parent forms, namely 2,4-D and MCPA respectively, in plants by Knoop (1904, 1931) β-oxidation of the side-chain. The enzyme systems concerned, which are present in the plant-cell glyoxysomes, are responsible for fatty acid catabolism, and their adoption in herbicide metabolism might be seen as an extension of their customary role in the intermediary metabolism and economy of plants. Clearly, the development of 2,4-DB and MCPB (see also III. 6) opened up fresh possibilities for the translocation of 2,4-D and MCPA activity, and the differential susceptibility of plant species to these aryloxyalkanoic acids emphasized their usefulness as (selective) herbicides, particularly in legume crops (Wain, 1954, 1955*a*, *b*, 1957).

In addition, the limited β-oxidation of 2,4-DB in the tops of big leaf maple in comparison with the rapid β-oxidation in the roots, coupled with the rapid metabolism of the 2,4-D released, helps to explain the resistance of this species to the herbicide and the efficacy of 2,4-DB, compared with 2,4-D and 2,4,5-T (see below), for the protection of big leaf maple (Norris & Freed, 1966*b*).

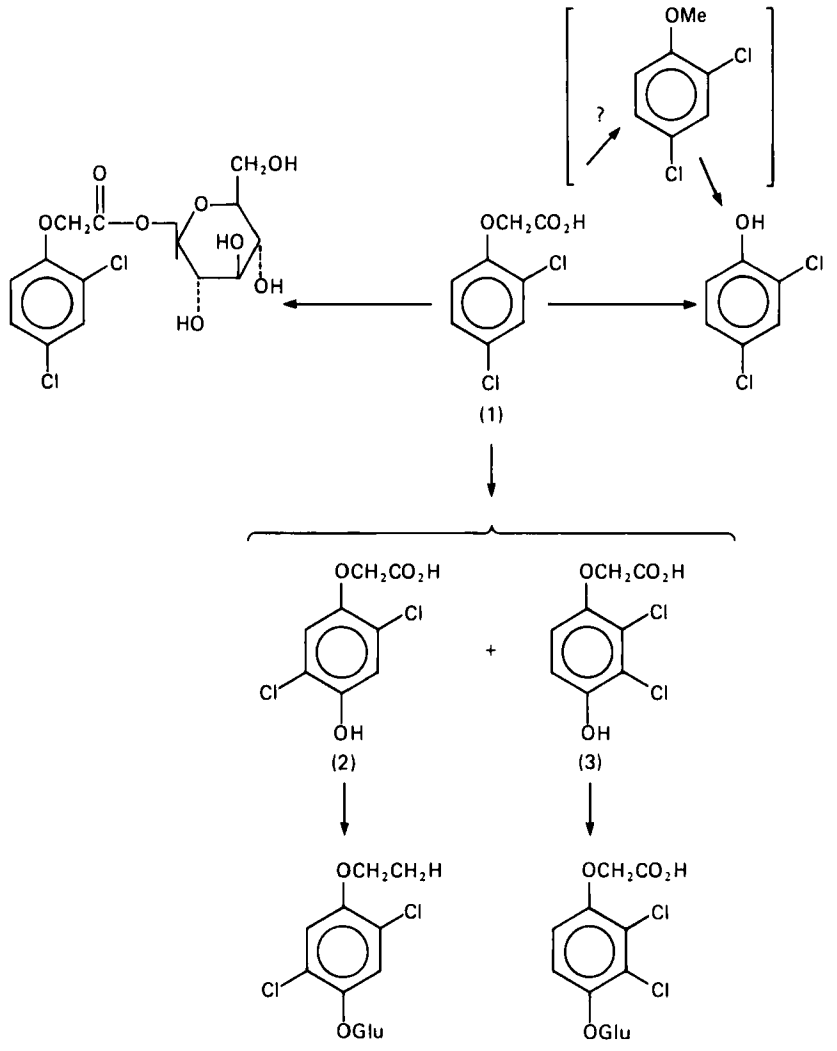
Activation of the *Avena fatua* herbicides (for example, the diclofop esters) is effected by carboxylesterase-catalysed hydrolysis into diclofop acid, which is the phytotoxic form of these herbicides (Shimabukuro, Walsh & Hoerauf, 1979).

(2) *Detoxification*

In the case where the actual herbicide molecule is the biologically active agent, a high activity of herbicide-metabolizing enzymes in treated plants follows resistance to phytotoxicity in the species concerned. For example, the rapid metabolism of aryloxyalkanoic acids by some cereal plants may contribute significantly to their selectivity, which otherwise might seem to relate solely to a limiting rate of absorption of these substances.

(*i*) *Plant regulatory aryloxyalkanoic acids*

Rapid metabolism and detoxification is significant to the selectivity shown by aryloxyalkanoic acids between dicotyledonous species and to the few cases of selectivity between some graminaceous species which have been reported. In this connection, the stepwise degradation of the side-chain, with the release of the carboxyl C-atom as CO_2 occurring twice as fast as that of the methylene C-atom as CO_2 may correlate with the tolerance of red currants (Ribes sativum) (Luckwill & Lloyd-Jones, 1960*a*), Cox's



Scheme 1

Orange Pippins (Luckwill & Lloyd-Jones, 1960*b*), McIntosh apples (Edgerton & Hoffman, 1961) and the garden lilac (Luckwill & Lloyd-Jones, 1960*b*) to 2,4-D. The red currant is also relatively resistant to MCPA, which it decarboxylates rapidly, but it is susceptible to 2,4,5-T despite the fact that this substance is decarboxylated as rapidly as 2,4-D and MCPA are. Luckwill & Lloyd-Jones (1960*b*) therefore suggested that the end-product of side-chain degradation, namely 2,4,5-trichlorophenol may be responsible for injury to the 2,4,5-T treated red currants, which showed different effects compared with the similarly treated black currants, which were unable to effect side-chain degradation. Formation of chlorophenols might also be responsible for the effects of MCPA on red currants as well as for the high toxicity both of MCPA and of 2,4,5-T towards strawberries (Luckwill & Lloyd-Jones, 1960*b*; Leafe, 1962). In general, the side-chain degradation of aryloxyalkanoic acids is not considered to be an important reaction process in the metabolism of these herbicides in plants (Scheme 1),

although it does contribute significantly to the detoxification of these herbicides in specific plants like the red currant and strawberry, (Loos, 1975).

The rapid metabolism of 2,4-D in the roots of the big leaf maple (*Acer macrophyllum*), its slow rate of metabolism in the leaves and shoots (Norris & Freed, 1966*a*) and its low rate of translocation (Fertig *et al.* 1964; Watham, Corbin & Waldrep, 1972) provide some explanation for the resistance of this species to the action of foliarly applied 2,4-D. Whilst such treatment may kill the tops of the trees, the roots survive and bring about regeneration. In comparison, the big leaf maple roots metabolized 2,4,5-T less efficiently, but as this compound was also poorly translocated, it was relatively ineffective (Fertig *et al.*, 1964; Norris & Freed, 1966*a*; Wathana *et al.*, 1972). Neidermayr & Nalewaja (1969) attributed the resistance of *Silene noctiflora* to 2,4-D to aryloxyalkanoic acid metabolism in the roots, but not in the tops, and to root excretion.

Under certain circumstances, enzyme blocking may be valuable. Thus, whilst the persistent dicotyledonous weed, *Galium aparine* oxidizes rapidly both acyl C-atoms of MCPA, oxidation is blocked completely by replacement of MCPA by the branched chain 2-propionic acid homologue, MCPP. Accordingly, MCPP may be used to control this weed (Leafe, 1962).

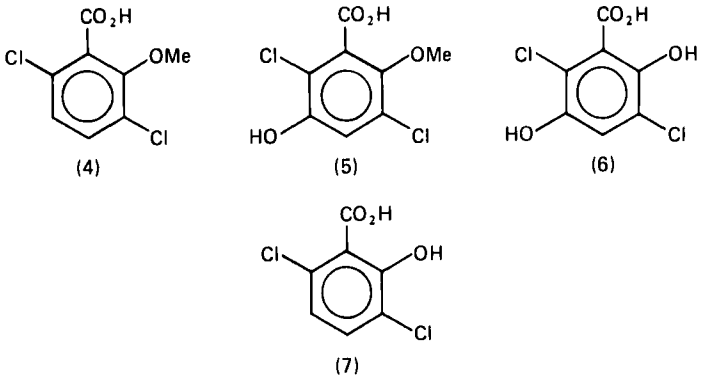
Finally, in treated barley, oats and wheat, but not in *Fagopyrum esculentum* and maize, ring hydroxylation of 2,4-D (1) (Scheme 1) produced 2,5-dichloro-4-hydroxyphenoxy-acetic acid (2) as principal metabolite together with the 2,3,-dichloro-4-hydroxy derivative (3) as a minor product both in the shoots and in the roots (Bristol, Ghanium & Oleson, 1977; Feung *et al.*, 1978), which were found to be free from plant-growth activity (Hagin, Linscott & Dawson, 1970; Hamilton *et al.*, 1971). This implies, in barley, oats and wheat, high activity of 2,4-D *p*-hydroxylase (Makeev, Makoveichuk & Chkanikov, 1977), which causes hydroxylation-induced migration of the Cl atom in position-4 of the 2,4-D ring (Loos, 1975; Feung *et al.*, 1978). Ring hydroxylation of (1) has also been found (Feung, Hamilton & Whitham, 1971; Feung *et al.*, 1978) in haricot bean and soyabean plants.

(*ii*) *The rest of the herbicides*

There are numerous cases, apart from those concerning the aryloxyalkanoic acids [III. 2(i)], in which species differences in herbicide metabolism coincide with and may account for the selectivities that have been found.

It is important in this context that microsomal preparations from plants have been found to catalyse key reactions in the anabolism of plant hormones, flavonoids, indole alkaloids, lignins, steroids and tannins as well as in intermediary lipid metabolism. The suspected presence of cytochrome *P*-450 in such microsomal preparations has been shown by CO-binding and by the fact that light at 450 nm reverses the CO inhibition (Murphy & West, 1974; Markham, Hartman & Parke, 1972; Cotte-Martinon, Yahiel, & Ducet, 1974; Potts, Weklych & Conn, 1974; Yahiel, Cotte-Martinon & Ducet, 1974; Rich & Bendall, 1975; Makeev *et al.*, 1977). Thus, plant mixed-function oxygenases resemble the corresponding mammalian systems, which are more fully characterized. The link with herbicide metabolism, however, has been demonstrated only recently, and there have been isolated and partially characterized:

(i) an *N*-demethylase from etiolated cotton, which catalyses the *N*-demethylation of *N*,*N*-dimethyl phenylureas (Frear, Swanson & Tanaka, 1969; 1972),



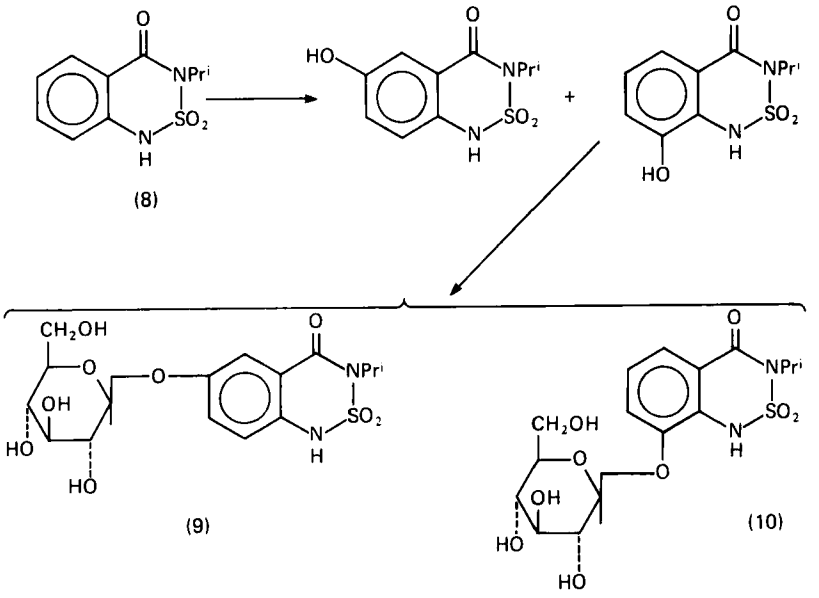
Scheme 2

(ii) a 2,4-D *p*-hydroxylase from cucumber and pea leaves (Makeev *et al.*, 1977) and (iii) a metamitron deaminase from sugar-beet leaves (Fedtke & Schmidt, 1979).

Many of the products of herbicide metabolism in plants, to which there is considered to be mixed-function oxidase involvement, are strictly similar to their metabolic counterparts in mammals in which the hepatic mixed-function oxydases are known to have participated. Furthermore, in certain cases (Dauterman & Muecke, 1974; Frear & Swanson, 1976; Nelson *et al.*, 1977; Chen & Casida, 1978; Foster, Khan & Akhtar, 1979), the products of herbicide metabolism in plants have been shown to be identical to those obtained in experiments with mammalian hepatocyte mixed-function oxygenases in vitro.

Ring hydroxylation is involved in the metabolism and selectivity of the benzoic acid herbicide, dicamba (4) (Scheme 2) (Broadhurst, Montgomery & Freed, 1966), which does not kill wheat nor *Poa annua*. The 5-hydroxy derivative (5) is the principal metabolite in barley, maize and wheat, and 3,6-dichlorosalicylic acid (7) is a very minor metabolite (Ray & Wilcox, 1967; Chang & Vanden Born, 1971*b*). In addition, 3,6-dichlorogentisic acid (6) was also detected in young weed plants treated with (4) (Wilson & Ray, 1967). Rapid (4) metabolism to which the glycosidation of all three metabolites may be a contributing factor in tolerant plants like wheat, compared with limited metabolism in the susceptible *Brassica kaber* and *Fagopyrum tartaricum* species may account for herbicide selectivity (Chang & Vanden Born, 1917*a*, *b*; Quimby & Nalewaja, 1971).

The metabolism of the closely related chloramben does not, however, involve ring-hydroxylation, and selectivity appears to depend on the different rates at which various plant species and tissues either detoxify and solubilize this herbicide as *N*-glucoside (Colby, 1965) and glucose ester (Frear, *et al.*, 1978) conjugates or immobilizes it as insoluble, bound complexes (Stoller & Wax, 1968; Stoller, 1969; Frear *et al.*, 1978). Thus, high levels of chloramben *N*-glucoside and low levels of chloramben glucose ester and unmetabolized herbicide were found in tolerant plants, such as *Ipomoea hederacea*, snapbean (*Phaseolus vulgaris*), soyabean and squash (*Cucurbita* spp.) as well as in ones of intermediate tolerance like cucumber and maize, whereas high levels of chloramben glucose ester and unmetabolized herbicide and low levels of the *N*-glucoside were associated with the chloramben-susceptible plants such as barley,



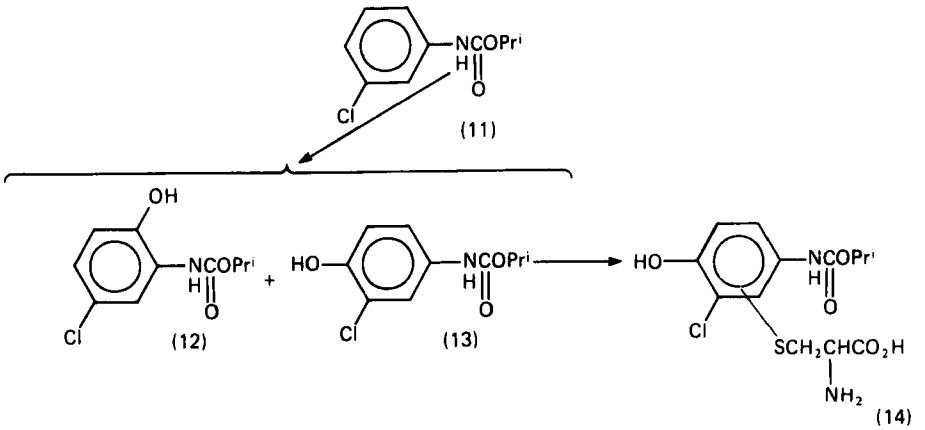
Scheme 3

Abutilon threophrasti, *Setaria faberi* and *Echinochloa* species (Frear *et al.*, 1978). Formation of high concentrations of chloramben glucose ester in susceptible plants may be an important contributive factor to effective phytotoxicity in those species, as this glucose ester is readily hydrolysed to the parent herbicide. Bound residues of chloramben were present both in resistant and susceptible species (Frear *et al.*, 1978).

Metabolism of bentazone (8) (Scheme 3) in plants involves successive aryl ring-hydroxylation and glycosidation. Tolerant maize, rice, soyabean, navybean (*Phaseolus vulgaris*) and *Echinochloa colonum* rapidly metabolize (8) with the accompanying accumulation of large amounts of water-soluble metabolites in their tisses, whereas the susceptible weeds, such as *Cirsium arvense*, *Cyperus serotinus*, *Eleocharis kuroguwai*, *Sagittaria pygmaea* and *Solanum nigrum*, do not metabolize this herbicide (Mahoney & Penner, 1975; Mine, Miyakado & Matsunaka, 1975; Penner, 1975). Thus, species differences in the rate of ring-hydroxylation seem to account for (8) selectivity. Rice afforded the glucoside (9) of the 6-hydroxy derivative as major metabolite (Mine *et al.*, 1975; Otto *et al.*, 1979), and soyabean plants gave glucosides (9) and (10) of both the 6- and 8-hydroxy derivatives (Otto *et al.*, 1979).

Hydroxylation is important to the metabolism in plants of propham, which is used for grass control in sugar-beet crops. Thus, propham metabolism in the Moapa variety of alfalfa, grown in culture, yielded conjugates of both isopropyl 2- and 4-hydroxycarbanilates (ring hydroxylation) and 1-hydroxy-2-propyl carbanilate (aliphatic hydroxylation) (Zuriqiyah, Jordan & Jolliffe, 1976) (see also Still & Mansager, 1975; Burt & Corbin, 1978). Other work (Still & Mansager, 1973*b*; Burt & Corbin, 1978) seemed to infer a faster rate of metabolism and a simpler hydroxylation pattern in the more resistant soyabean and sugar-beet species.

In resistant plants, like soyabean (Still & Mansager, 1971; Still, Rusness & Mansager, 1974), the major chlorpropham (11) (Scheme 4) metabolite was isopropyl 5-chloro-



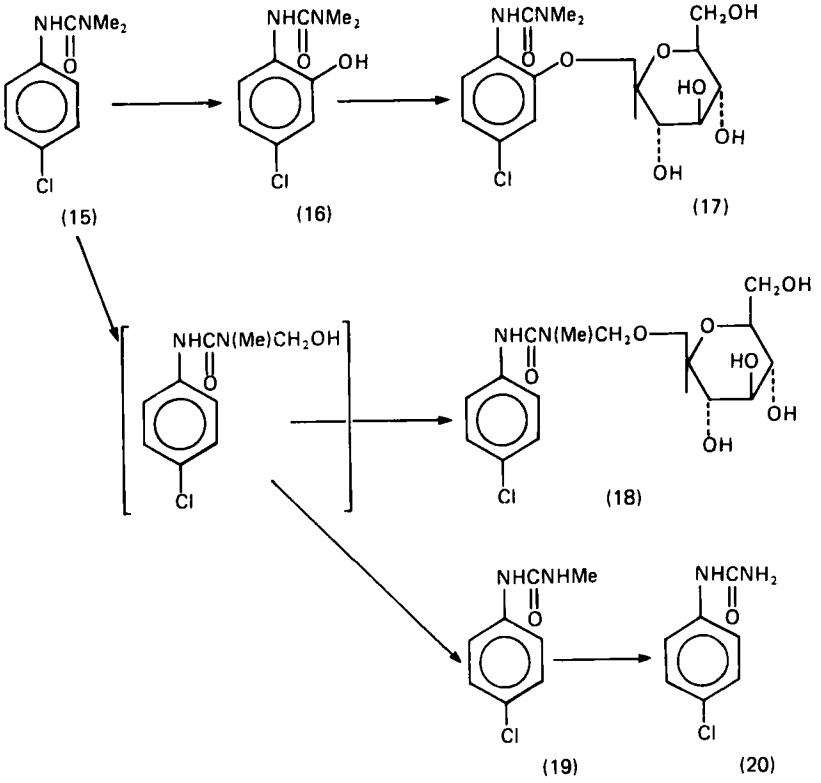
Scheme 4

2-hydroxycarbanilate (12). But, in susceptible species, like cucumber (Still & Mansager, 1973*a*), the predominant metabolite was 4-hydroxy-3-chlorocarbanilate (13). Detailed study (Still *et al.*, 1974) of the effect of (11) metabolites on plant intermediary metabolism showed that susceptibility to (11) might be a function of the rate of ring hydroxylation, or of the rate of the conjugation of ring-hydroxylation products. In this connexion, it is also interesting that a *S*-cysteinyl derivative (14) of (13) was formed as far as is known only in oats (see below).

Unidentified perfluidone water-soluble and -insoluble products were the main metabolites obtained from treated groundnut (*Arachis hypogaea*) seedlings, harvested after growth in culture (Lamoureaux & Stafford, 1977). The identification of 1,1,1-trifluoro-*N*-[4−{(3-hydroxyphenyl)sulphonyl}*o*-tolyl]methanesulphonamide in the water-soluble fraction from the leaves shows that one metabolic pathway for perfluidone involves ring hydroxylation and glycosidation (Lamoureaux & Stafford, 1977).

Finally, ring hydroxylation of monuron (15) (Scheme 5), to give 2-hydroxymonuron (16) and the corresponding 2-*O*-β-D-glucoside (17), contributes to (15) metabolism in bean (Lee & Fang, 1973; Lee, Griffin & Fang, 1973), cotton (Frear & Swanson, 1974) and maize (Lee *et al.*, 1973) seedlings, but oxidative-*N*-demethylation to give metabolites (18)–(20) is also important (see below). Similarly, ring hydroxylation contributes to the metabolism of monolinuron in spinach (Schupan & Ebing, 1975).

Deamination. In carrots and potatoes, metribuzin (21) (Scheme 6) underwent oxidative deamination to afford 6-*tert*-butyl-1,2,4-triazine-3,5(2H,4H)-dione (24) via the stable intermediates 6-*tert*-butyl-3-methylthio-1,2,4-triazine-5H(4H)-one (22) and 4-amino-6-*tert*-butyl-1,2,4-triazine-3,5(2H)-dione (23) (Prestel *et al.*, 1976). The end-product (24) was present both as a conjugate and bound to cell components (Prestel *et al.*, 1976). Water-soluble metabolites were major products of catabolism in several species and, in tomatoes, the major (21) polar metabolite was identified as malonyl metribuzin *N*-β-D-glucoside (26) with metribuzin *N*-β-D-glucoside (25) as a minor intermediate (Frear *et al.*, 1983). Biosynthesis of (25) was effected with a partially purified UDP-glucose: metribuzin-*N*-glucosyl transferase from tomato leaves. These authors (Frear *et al.*, 1983) found a feasible correlation between foliar UDP-

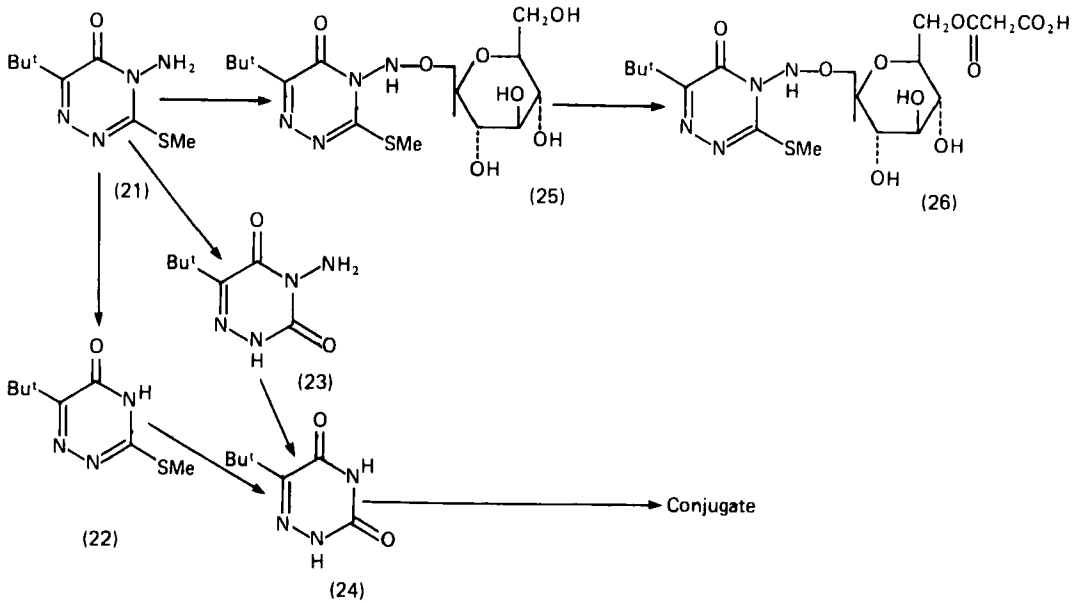


Scheme 5

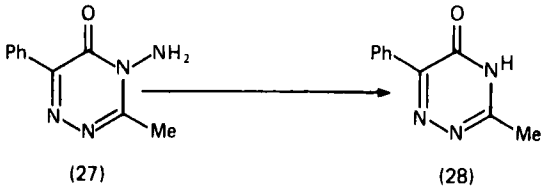
glucose:metribuzin *N*-glucosyl transferase and differences in resistance of selected tomato seedling cultivators to (21). Interestingly the trimethylpyruvic acid semicarbaz one degradation-product of (24), was found amongst the polar constituents of above-ground potato plants, treated with (21), during the second and third growing seasons (Prestel *et al.*, 1976). Work with resistant and susceptible cultivars of tomatoes and soyabeans is discussed in Section III. 4.

Fedtke & Schmidt (1979) have reported the isolation and partial characterization of a microsomal metamitron (27) (Scheme 7) deaminating enzyme from the leaves of (27) resistant sugar-beet. Deamination, which occurs under reducing conditions in which substances such as glutathione, cysteine, dithionite, ascorbate, etc. serve as electron donors, requires the presence of cytochrome *c* and the cofactors FMN, FAD or DCPIP and, although the reduction of NADPH and NADH as donors do not appear to have been investigated, the metamitron-deaminating enzyme behaves as a mixed-function oxidase.

Plants tolerant to (27), for example *Mercurialis annua* and sugar-beet, showed initial inhibition to photosynthesis, but they rapidly recovered, due to the biotransformation of (27) into the deamination product (28), which is a practically inactive metabolite. Susceptible plants, like *Amaranthus retroflexus*, showed a much slower rate of (27) deamination (Schmidt & Fedtke, 1977). Thus, the capacity of plants to deaminate (27) seems to be the main factor determining plant resistance to (27).



Scheme 6



Scheme 7

O-Dealkylation. More efficient *O*-demethylation of metoxuron has been postulated (Vassiliou and Muller, 1978) in the resistant carrot and parsnip plants than in susceptible species, like celery, caraway (*Carum carvi*) and parsley (*Petroselinium crispum*). Inhibition of photosynthesis by metoxuron was reversible in the resistant crop plants, but not in the sensitive species. Thus, a positive correlation seems to have been established, in this case, between resistance and *O*-demethylation.

On the other hand, the *O*-demethylation of dicamba in plants (Broadhurst, Montgomery & Freed, 1966; Ray & Wilcox, 1967; Chang & Vanden Born, 1971*b*) appears to be a very minor metabolic pathway (see above).

N-Dealkylation. Oxidative *N*-dealkylation is significant to the plant metabolism of *N,N*-dimethyl-and *N*-methyl-phenylurea, *sym*-triazine and dinitroaniline herbicides.

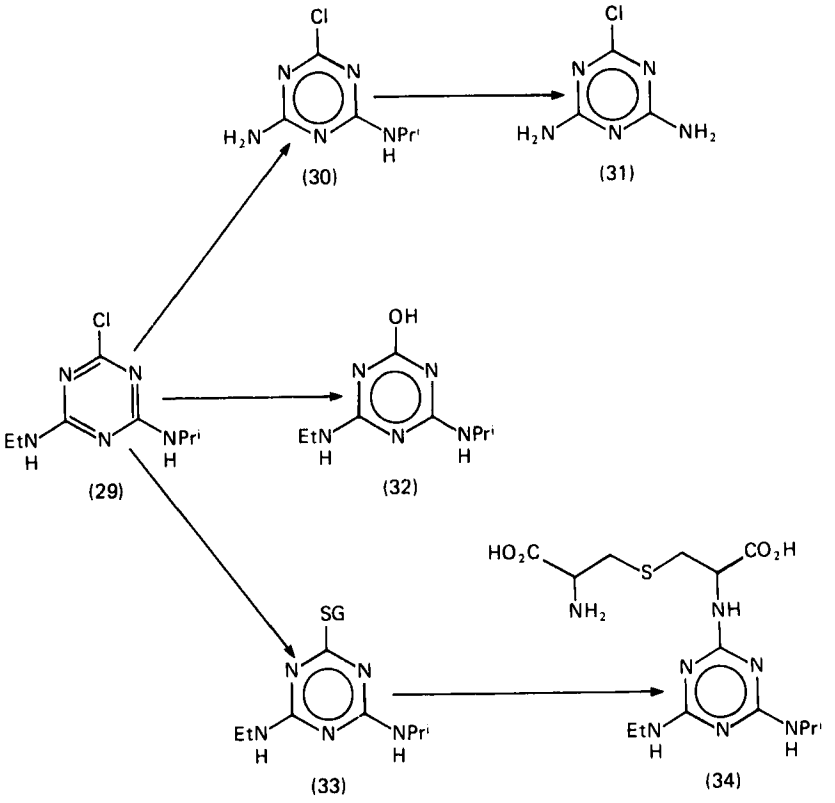
Cotton *N*-demethylase (Frear *et al.*, 1969, 1972) catalyses the demethylation only of the *N,N*-dimethyl phenylurea herbicides, such as diuron and monuron (see above), but not of an *N,N*-dimethyl-thiadiazole urea analogue (Lee & Ishizuka, 1976). Hence the phenyl ring appears to be spatially important to the reaction of this enzyme. Furthermore, replacement of the *C1*-atom, which is present in 4-position of the phenyl ring, both of diuron and monuron, either by a methyl group as in chlortoluron or by

a methoxy group as in metoxuron, leads to the oxidative metabolism of these groups in those compounds (Vassiliou & Muller, 1978; Gross, *et al.*, 1979) rather than to oxidative *N*-demethylation. Formation of the unstable methylol derivative (the unnumbered formula in square brackets in Scheme 5) represents the first step in *N*-demethylase *N*-demethylation of monuron by the pathway (15)–(19). This methylol has been isolated as the *O*-glucoside conjugate (18) from cotton seedlings (Tanaka, Swanson & Frear, 1972*a*, *b*). *N*-Demethylation of *N*-methyl or of *N*-methyl-*N*-methoxy phenylurea herbicides is also effected through initial formation of methylol intermediates (Kuratle, Rahn & Woodmansee, 1969; Nashed & Ilnicki, 1970; Collet & Pomp, 1974; Pont *et al.*, 1974; gross *et al.*, 1979). Work with the fungus, *Cunninghamella echinula* showed that the methylol derivatives of linuron and monolinuron, unlike those of diuron and monuron, were stable (Tillmans *et al.*, 1978). The oxidative *N*-dealkoxylation of linuron and monolinuron has also been found in several plant species. Another point with regard to the specificity of the cotton *N*-demethylase (Frear *et al.*, 1969, 1972) is that other herbicides, like diphenamid, which undergoes *N*-dealkylation in plants, are not *N*-dealkylated by this enzyme.

Differential rates of *N*-demethylation in plants contribute to the selectivity of substituted phenylurea herbicides (Smith & Sheets, 1967; Swanson & Swanson, 1968*a*; Lee & Fang, 1973; Schupan & Ebing, 1978) with the proviso that in these phenylureas where there is a methyl group, as in chlorotoluron, or a methoxy group, as in metoxuron, in 4-position of the phenyl ring, the oxidation of those groups predominates over *N*-demethylation of the *N*,*N*-dimethylurea residue. Thus, chlortoluron metabolism in chlortuloron-resistant wheat seedlings afforded the 4-hydroxymethylphenyl- and 4-carboxyphenyl-derivatives, which were further conjugated with glucose (Gross *et al.*, 1979). On the other hand, *O*-demethylation of metoxuron in metoxuron-resistant carrot and parsnip plants is the principal metabolic pathway for this herbicide in these species (see above), whereas *N*-demethylation of the *N*,*N*-dimethylurea residue is the dominant metabolic pathway in the intermediately resistant caraway (*Carum carvi*) plants (Vassiliou & Muller, 1979).

N-Dealkylation of the *sym*-triazine herbicides, for example, atrazine (29) (Scheme 8) has been shown (Shimabukuro, Kadunce & Frear, 1966; Shimabukuro, 1967*a*, *b*, 1968; Shimabukuro & Swanson, 1969, 1970; Roeth & Lavy, 1971) to give important metabolites (30), (31) in plants, and there is indirect evidence for plant mixed-function oxydase involvement. Thus, the injury caused by this herbicide to soyabean plants was enhanced by the application of a combination atrazine and piperonyl butoxide herbicide (Leavitt, Rubin & Penner, 1978), possibly because of the inhibition of the mixed-function oxydase system responsible for *N*-dealkylation. In addition, this reaction has been found to be catalysed by rat-liver (Dauterman & Muecke, 1974) and chicken-liver (Foster *et al.*, 1979) microsomes.

Whilst benzoxazinone-mediated hydrolysis and conjugation with glutathione (Shimabukuro, Lamoureaux & Frear, 1978) are undoubtedly the two metabolic pathways (Scheme 8), which are essential to the resistance of plants to *sym*-triazine herbicides (see below), *N*-dealkylation appears to occur in varying degree in higher plants. Thus, for example, removal of the *N*-ethyl group of atrazine affords a partially phytotoxic metabolite and removal both of the *N*-ethyl group and of the *N*-isopropyl one gives a completely inactive metabolite (Shimabukuro, 1967*a*). In summary, *N*-alkylation is



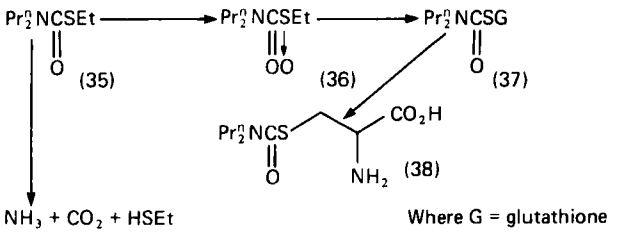
Where G = glutathione

Scheme 8

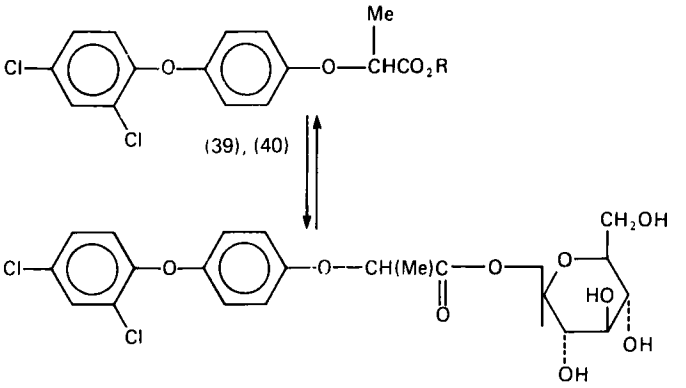
not considered to be a mechanism that confers complete resistance to *sym*-triazine herbicides to plants, but it may contribute to the selectivity of *sym*-triazines in comparatively resistant species. Thus, *N*-dealkylation is thought to contribute to the resistance of such plants as cotton and peas to atrazine (Shimabukuro, 1967*a*; Shimabukuro & Swanson, 1969*a*). In this connection, recent work (Gressel, Shimabukuro & Duysen, 1983) with *Senecio vulgaris* biotypes, which developed partial tolerance to *sym*-triazine herbicides, did not explain the resistance of *Senecio* to atrazine, but showed that *N*-dealkylation of the *sym*-triazines occurred more extensively than had been previously described.

Whilst bentazone (8) possesses an *N*-isopropyl group, rapid ring hydroxylation (Scheme 3) occurs at the expense of *N*-dealkylation in resistant species.

N-Dealkylation represents the main metabolic pathway in plants for dinitroaniline herbicides (Golab *et al.*, 1967; Biswas & Hamilton, 1969; Marquis *et al.*, 1979; Dixon & Stoller, 1982). A mixed-function oxydase system appears to be implicated, as the *N*-dealkylations are mediated by rat-liver microsomes (Nelson *et al.*, 1977) and by crude enzyme preparations from groundnut (*Arachis hypogaea*) and sweet potato (*Ipomoea batatas*) seedlings (Biswas & Hamilton, 1969). Trifluralin shows selective action for control of *Alopecurus myosuroides* in cereals (Rahman & Ashford, 1970).



Scheme 9



(41)

Scheme 10

The greater resistance of the roots of soyabean compared with those of maize to fluchloralin injury was attributed (Marquis *et al.*, 1979) to a difference in the rate of fluchloralin metabolism in the roots of those species.

Metolachlor was metabolized at a significantly faster rate by maize, which was tolerant to metolachlor injury, than by the susceptible *Cyperus esculentus*, and maize produced more metolachlor metabolites (Dixon & Stoller, 1982).

Sulphoxidation. EPTC sulphoxide (36) (Scheme 9) has been identified as a major metabolite of EPTC (35) metabolism in maize (Hubbel & Casida, 1977; Carringer, Rieck & Bush, 1978) and, in fact, the activation of thiocarbamate herbicides has been attributed to their sulphoxidation in plants (Casida, Gray & Tilles, 1974). Sulphoxidation was shown to occur in living mice and, in experiments with mouse-liver microsomes in vitro, to involve a mixed-function oxydase system (Casida *et al.*, 1975*a*). Because of the considerable difficulty in isolating and characterizing plant enzymes, no information is yet available on the catalysis of this reaction by plant mixed-function oxidases.

Whilst compound (36) has been found to be more phytotoxic than the parent herbicide (35) (Casida *et al.*, 1975*b*), (36) is very rapidly metabolized by glutathione conjugation (36)–(38), in tolerant plants such as maize.

In addition to reactions catalysed by mixed-function oxydases (*q.v.*), herbicide metabolism in plants involves several other reaction processes.

Ester hydrolysis. Thus, carboxylesterases are responsible for the hydrolysis of the phenoxy-phenoxy, diclofop-methyl (39; where R = Me) (Scheme 10) herbicide to the

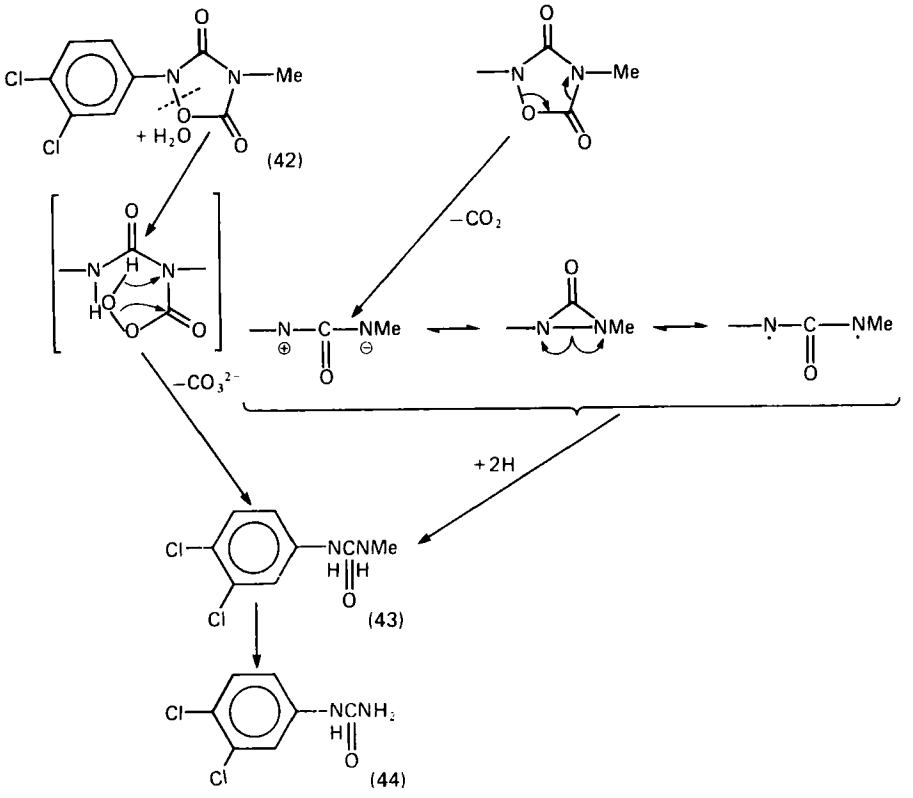
phytotoxic diclofop acid (40; where R = H) by wheat and *Avena fatua* seedlings (Shimabukuro *et al.*, 1979).

Species differences in herbicide metabolism have been considered to account for the selectivity of this herbicide (39; where R = Me) (Shimabukuro, *et al.*, 1979; Donald & Shimabukuro, 1980) between these species. Thus *Avena fatua* conjugated (40; where R = H) to give the ester glucoside (41), which may be hydrolysed to regenerate the phytotoxic acid (40), and this possibility helped to explain the susceptibility of this species for (39; where R = Me). In addition, an enzyme responsible for aryl hydroxylation in *Avena fatua* appears to have high affinity for the 4-chloro homologue of diclofop-methyl, and its limited capacity to rapidly hydroxylate (39; where R = Me) and (40; where R = H) contributed to the susceptibility of this species to diclofopmethyl compared with wheat (Gorecka, Shimabukuro & Walsh, 1981; Dusky, Davis & Shimabukuro, 1982; Jacobson & Shimabukuro, 1984).

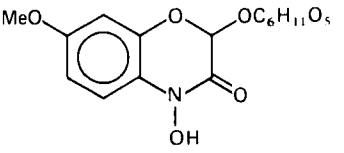
Amide hydrolysis. The hydrolysis of propanil has been investigated intensively, and the selectivity of this herbicide between, for example, resistant rice plants and the susceptible *Echinochloa crus-galli* (Table 1) has been attributed to its rapid hydrolysis in rice. Whilst this reaction was previously considered to involve the lactanilide oxidation-product (Yih, McRea & Wilson, 1968), subsequent investigations have established that direct hydrolysis, involving a specific aryl acylamidase, is preferred (Frear & Still, 1968; Tasi, 1974; Hoagland, 1978). The rice leaves contain sixty times as much of this enzyme as the *Echinochloa* leaves do (Frear & Still, 1968), and this differential accounts for the rapid hydrolysis of herbicide observed in rice seedlings and its virtual absence in the weed species. Enzymes similar to rice aryl acylamidase are present in tulip (Hoagland & Graf, 1972), *Taraxacum officinale* (Hoagland, 1975), and twenty other species of higher plant (Hoagland, Graf & Handel, 1974). Lettuce leaves were the most abundant source of this enzyme, and rice plants with four leaves had greater enzyme activity than those with less than four leaves (Ray & Still, 1975). Amide hydrolysis is unimportant to the fate of carbanilate, thiocarbamate and urea herbicides (Table 1) in plants.

At first sight, hydrolysis might be involved in the intriguing ring-fission of the 1,2,4-oxadiazolidine ring of methazole (42) (Scheme 11) in cotton and *Sida spinosa* to yield 1-(3,4-dichlorophenyl)-3-methylurea (43), but successive elimination of CO_2 and hydrogen abstraction may offer an alternative mechanism (Scheme 11). The product (43) is phytotoxic and is produced more rapidly in *Sida spinosa* than in cotton plants, but further *N*-demethylation to give 1-(3,4-dichlorophenyl) urea which is non-toxic, was faster in cotton plants (Butts & Foy, 1974). The fact that more (42)-related material was present in *Sida spinosa* than in cotton and that a greater proportion of this material was herbicidal in the weed species than in the crop plants helps to explain the selectivity of (42) between *Sida spinosa* and cotton (Butts & Foy, 1974).

Hydrolysis of sym-*triazines.* The *sym*-triazines undergo nucleophilic replacement of the 2-chloro substituent in the triazine ring to give the herbicidally inactive 2-hydroxy compounds and this reaction, which occurs primarily in the roots of resistant plants, has been considered to be important to the detoxification of atrazine in maize plants (Castelfranco, Foy & Deutsch, 1961; Hamilton & Moreland, 1962; Hamilton, 1964*b*; Tipton, Husted & Tsao, 1971; Willard & Penner, 1976). Although this hydrolysis occurs in vivo, it was recognised at the start as being a chemical (non-enzymic) reaction



Scheme 11



Formulae 45

process. Thus, simazine was found to be rapidly transformed by maize sap, but not by that of wheat and oats (Roth, 1957) into the inactive 2-hydroxy derivative (Castelfranco *et al.*, 1961). The 'maize-resistant factor' was soon identified as the 2-β-D-glucoside of 2,4-dihydroxy-3-keto-7-methoxy-1,4-benzoxazinone (45) (Roth & Knüsli, 1961; Hamilton & Moreland, 1962), and the corresponding aglycone is the compound involved with hydrolysis, and which is released enzymically in the plant from compound (45). The triazinyl ring of these herbicides is also important to the chemical hydrolysis, catalysed by benzoxazinones (Ioannou, Dauterman & Tucker, 1980).

Whilst the rate at which the 2-chloro-*sym*-triazines are hydrolysed into the corresponding 2-hydroxy derivatives may be correlated with benzoxazinone concentration present, this would not appear to be the only mechanism for the implementation of this reaction in plants. Thus, for example, sorghum and *Sorghum halepense* (Johnson grass), which do not contain the 'maize-resistant factor', generate the 2-hydroxy derivatives

upon treatment with *sym*-triazine herbicides. In addition, the presence of the 'maize-resistant factor' has been reported in some atrazine-susceptible species, such as wheat (Funderburk & Davis, 1963; Ashton & Crafts, 1973), but as the hydrolysis of *sym*-triazines occurs in the roots, the rapid translocation of these herbicides from the roots to the shoots may help to explain the lack of correlation of tolerance with benzoxazinone content in these plants.

In conclusion, whilst the benzoxazinone-catalysed hydrolysis of 2-chloro-*sym*-triazines undoubtedly contributes to the overall detoxification of, for example, atrazine, it may be inessential to plant resistance (see below).

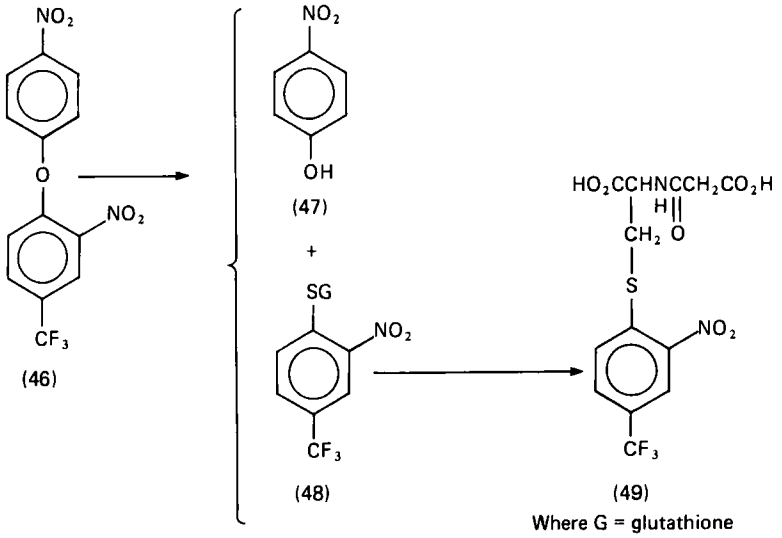
Glutathione conjugation. A triazinyl glutathione *S*-transferase enzyme, which is responsible for the conjugation of the 2-chloro-*sym*-triazines, atrazine (29) (Scheme 8), cyanazine and simazine with glutathione (Scheme 8), has been identified only in maize, sugar-cane, sorghum and *Sorghum halepense* (Frear & Swanson, 1970; Guddewar & Dauterman, 1979). The triazinyl glutathione *S*-transferase proved to be specific for 2-chloro-*sym*-triazines, and the *sym*-triazine herbicides with hydroxy-, methoxy- and methylthio-substituents in 2-position were unacceptable as substrates (Frear & Swanson, 1970; Guddewar & Dauterman, 1979). *N*-Alkyl groups were also important to enzyme activity, as the absence of an *N*-alkyl group led to diminished conjugation, and as 2-chloro-4,6-*bis*-amino-*sym*-triazine was the worst substrate.

Conjugation of atrazine with glutathione provides a major metabolic pathway (29)–(34) (Scheme 8), which is associated both with the detoxification and with the selectivity of this herbicide in resistant plant species (Shimabukuro, Swanson and Walsh, 1970). In fact, maize lines with a defective triazinyl glutathione *S*-transferase system were susceptible to atrazine (Shimabukuro *et al.*, 1971).

Maize is very resistant to atrazine (29) and employs all three metabolic pathways (Scheme 8) to detoxify this herbicide (Shimabukuro, 1967*a*, *b*; Shimabukuro, Lamoureux & Frear, 1978) but sorghum, which is also resistant, uses primarily glutathione conjugation and to a lesser extent *N*-dealkylation for its detoxification. Sorghum lacks the 'maize-resistant factor' (see above). Furthermore, other plants which are very or moderately susceptible to atrazine, such as oats, wheat and peas, lack the triazinyl glutathione *S*-transferase enzyme system (Frear & Swanson, 1970). Another susceptible crop plant, barley has but slight triazinyl glutathione *S*-transferase activity (Lamoureux, Stafford & Shimabukuro, 1972). These results show the importance of glutathione conjugation to the resistance of plants to atrazine.

As the glutathione conjugation of simazine is much slower than that of atrazine (Thompson, 1972), it would be expected, therefore, to contribute very little to the selectivity of simazine.

Chemically, the diphenyl ether herbicides are relatively unreactive, and the degree in which fission of the diphenyl ether bridge occurs in plants would seem to contribute to the wide-ranging spectrum of selectivity, which characterizes them. The discovery of an aryl glutathione *S*-transferase system in pea plants, which is responsible for the glutathione conjugation of fluorodifen (46) (Scheme 12) (Frear & Swanson, 1973; Shimabukuro *et al.*, 1973; Diesperger & Sandermann, 1979) was therefore important. This aryl glutathione *S*-transferase effects the fission of this herbicide to give *S*-(2-nitro-4-trifluoromethylphenyl)glutathione (48) and *p*-nitrophenol (47). After removal of the glutamic acid and glycine residues from (48) *S*-(2-nitro-4-trifluoro-



Scheme 12

methylphenyl)cysteine formed the malonyl derivative of *S*-(2-nitro-4-trifluoromethylphenyl)cysteine, namely (49) (Lamoureux & Rusness, 1983). The fact that nitrofen is also degraded by diphenyl ether fission in plants (Hawton & Stobbe, 1971) may suggest that, in different species, there are differences in the specificity of the aryl glutathione *S*-transferase enzymes concerned.

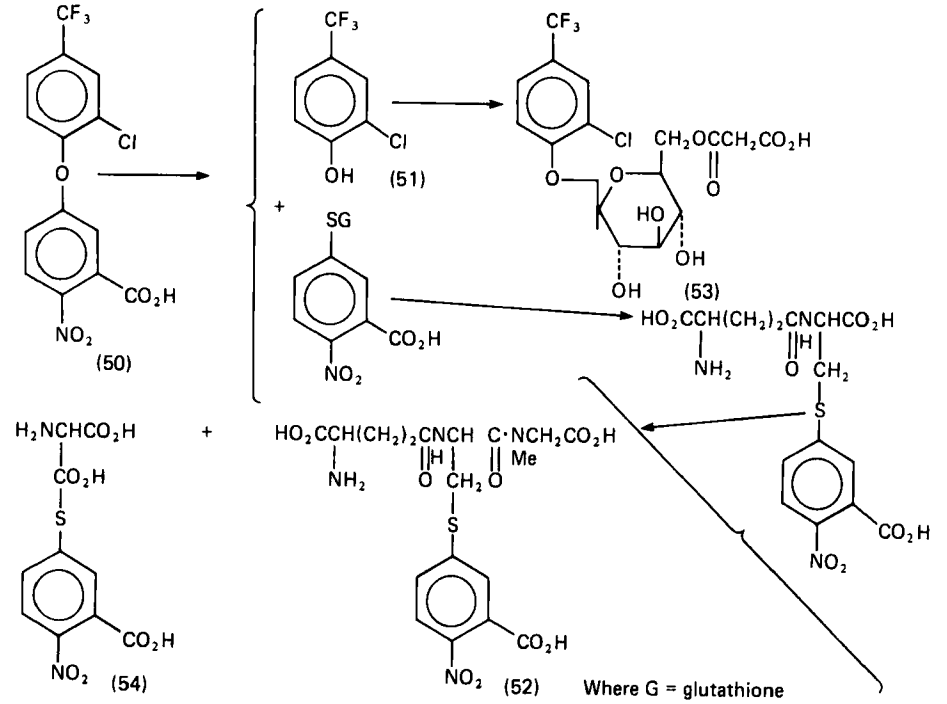
There is a strong supposition that the activity of a specific aryl glutathione *S*-transferase enzyme for conjugation with the 2-nitro-4-trifluoromethylphenyl-residue of herbicide (46) contributes to the resistance of cotton, pea, groundnut and soyabean plants to (46) (Frear & Swanson, 1973; Shimabukuro *et al.*, 1973).

Rather similarly, a specific aryl glutathione *S*-transferase effects the fission of acifluorfen (50) (Scheme 13) in the excised leaves of soyabean plants to give the malonyl O-β-D-glucoside (53) of 2-chloro-4-trifluoromethylphenol (51) as a major metabolite together with the homoglutathione conjugate, namely *S*-(3-carboxy-4-nitrophenyl)-γ-glutamyl-cysteinyl-β-alanine (52), and the corresponding cysteine conjugate, *S*-(3-carboxy-4-nitrophenyl)cysteine (54) (Frear, Swanson & Mansager, 1983).

On the other hand, bifenox is unmetabolized by shoot-tissue macerates of maize, soyabean and *Abutilon theophrasti* (Leather & Foy, 1977), and its selectivity between the tolerant maize and soyabean plants and the susceptible weed species seems to depend on the restriction of bifenox to the primary and secondary leaf veins of the crop plants compared with its greater mobility in *Abutilon theophrasti* and its distribution throughout the leaf tissues of that species (Leather & Foy, 1978).

Conjugation of the aromatic ring of 4-hydroxychlorpropham (13) (Scheme 4) with cysteine was found to be catalysed by a partially purified, soluble enzyme from the shoots of oats (*Avena fatua*) in vitro (Rusness & Still, 1977*a*, *b*), and the feasible involvement of glutathione was excluded, as glutathione does not serve as substrate for the biosynthesis of the *S*-cysteinyl derivatives (14) in vivo (Still & Rusness, 1977)

As far as is known, (14) is formed only in oats, which is susceptible to chlorpropham (11). The significance of the formation of (14) to crop selectivity is as yet unknown.



Scheme 13

The biologically active sulphoxide (36) (Scheme 9) of EPTC (35) was conjugated chemically (non-enzymically) with glutathione in vitro to give *S*-carbamyl glutathione (37) (Hubbell & Casida, 1977; Leavitt & Penner, 1979), and work in maize plants has indicated that (36) is conjugated with glutathione in the roots of that species. Because of injury caused to maize seedlings by the commercial usage of EPTC, various antidotes have been developed (III. 4).

Glycosidation. Naturally occurring glycosides, such as the anthocyanins, cyanogenic glycosides, *Digitalis* glucosides and saponins, are well-known (Paech, 1950), and the capacity of plants for glycosidation extends to exogenous herbicides. Not only do several herbicides form glycosides *per se*, but glycosidation follows almost invariably ring hydroxylation (see above). Besides conferring greater water-solubility and increasing the rate of translocation, glycosidation is also associated with detoxification and, in this connection, the glycosides of acids, amines and phenols seem to represent end-products for the metabolic pathways concerned.

2,4-D is a case in point, not only is ring hydroxylation followed by glycosidation (see above), but 2,4-D itself forms an ester glucoside directly (Scheme 1) in many species, including soyabeans (Feung *et al.*, 1971, 1973, 1976, 1978), peas (Chkanikov *et al.*, 1976), maize (Montgomery, Chang & Freed, 1971), barley (Feung *et al.*, 1971), clover (Bristol *et al.*, 1977), cucumbers (Chkanikov *et al.*, 1976) and beans (Montgomery *et al.*, 1971). Whilst formation of the ester glycoside undoubtedly contributed to detoxification, as it is formed so widely and in plants of varying degrees of susceptibility, its occurrence may contribute very little to the resistance of the species concerned (see above).

Biosynthesis of chloramben *N*-β-D-glucoside represents a significant detoxification pathway in all of the species investigated (Stoller & Wax, 1968; Frear *et al.*, 1978), and in resistant species the immobile and unreactive chloramben *N*-β-D-glucoside remains as a non-herbicidally active terminal substance. In susceptible species, however, *N*-glucoside biosynthesis is substantially diminished, and biosynthesis of the *O*-glucose ester competes effectively for free chloramben (Frear *et al.*, 1978).

There are conflicting accounts about an *N*-glycoside derivative of amitrole, which was first proposed by Rogers (1957), but which was subsequently thought to be an artifact (Carter, 1975). Again it was said (Stoller & Wax, 1968) that smaller amounts of free amitrole were present in the resistant soyabean, squash and *Convolvulus tricolor* than in the susceptible *Abutilon theophrasti* and *Stellaria* species, and resistance was attributed (perhaps wrongly with hindsight) to the glycosidating system.

Direct *O*-glucosidation appears to be the main metabolic pathway for maleic hydrazide in tobacco plants (Frear & Swanson, 1978) as well as in the injected *Acer saccharinum*, *Platanus occidentalis*, (Domir, 1978), *Quercus rubra* (Domir, 1980*a*) and *Ulmus americana* (Domir, 1980*b*) tree seedlings, in which it was used to retard the growth of suckers. In contrast to the structurally-related maleic hydrazide, daminozide was entirely unmetabolized after injection into *Acer saccharinum*, *Platanus occidentalis* (Domir & Brown, 1978), *Quercus rubra* (Domir, 1980*a*) and *Ulmus americana* (Domir, 1980*b*) tree seedlings. It is used in orchards to improve the quality of the fruit.

Formation of *O*- and *N*-glycoside conjugates of chloramben and chlorpropham, which regulate the phytotoxicity of these herbicides, serve as a basis for selectivity (see above). Limited investigation has shown, however, that herbicide glycosides can undergo further reaction in plants (Haque, Schupan & Ebing, 1978). Thus, in spinach plants, treated with the previously synthesized *O*-β-D-glucoside of hydroxymonolinuron via their roots, biotransformation occurs with regeneration of hydroxymonolinuron and the formation of *N*-demethylated monolinuron and 4-chlorophenylurea as major metabolites (Haque *et al.*, 1978). Similarly, in the excised tissues both of barley (susceptible) and soyabean (resistant) plants, the inactive *O*-ester glucoside of chloramben readily regenerated active herbicide (Frear *et al.*, 1978). Furthermore, in abscised cotton leaves, the *O*-ester glucoside of 3-phenoxybenzoic acid formed a polar metabolite, which was considered to be the glucosylarabinose ester that was undetected in cotton leaves treated with 3-phenoxybenzoic acid (More, Roberts & Wright, 1978).

Concluding Remarks. The foregoing discussion shows that at any rate in many cases herbicide selectivity parallels species differences in metabolism and plant-enzyme activity. Optimum selectivity occurs, where there is a fast turnover of herbicide in the crop plants commensurate with resistance, and where the weed species register the full brunt of unmetabolized herbicide so that they succumb.

Metabolic regulation would appear to be exerted over the fate of herbicides in plants through genetic control of the rate of enzyme synthesis. Clearly, the rate of a particular metabolic sequence depends on the concentration of the active form of each enzyme, which in turn depends on its turnover, and the rate of biosynthesis of a given enzyme in vivo may vary widely depending upon the prevailing conditions. The enzymes which effect herbicide metabolism in plants appear to be constitutive ones, as they are present in the cellular microsomal sedimentation fraction of the various tissues in approximately

constant amounts, irrespective of whether the plants concerned had been treated with herbicide. This supposition would seem to be supported by the fact that the activities of plant mixed-function oxydases in particular species may be stimulated in vivo (III. 3), but the feasible intervention of adaptive enzymes in the fate of herbicides in plants cannot be ruled out.

Some of the cellular genes of resistant plant species modify the effect of herbicides in vivo to the extent in which they regulate their detoxification through metabolism, and such genes accordingly participate in an auto-defence mechanism against specific herbicides in the species concerned.

(3) *Stimulation of plant–enzyme activity in vivo*

As in the case of the induction of mammalian mono-oxygenase systems in vivo, some plant mixed-function oxygenases can also be induced by foreign compounds. Thus, for example, the activity of 2,4-D-*p*-hydroxylase [III. 2(ii)] in cucumber and pea plants was found (Makeev *et al.*, 1977) to be stimulated after treatment with 2,4-D. Furthermore, Reichhart *et al.*, (1980) discovered that both monuron and dichlorbenil, but not chlorpropham, increased the activity both of *trans*-cinnamic hydroxylase and of cytochrome *P*-450 in microsomal fractions, prepared from Jerusalem artichoke tubers (*Helianthus tuberosus*). These well-authenticated cases of the induction of plant mixed-function oxydases are reminiscent of those inductions in mammalian tissues by DDT, hindered phenolic antioxidants, polychlorinated biphenyls, etc.

The protection of maize plants by R-25788 (*N*,*N*-diallyl-2,2-dichloroacetamide) from injury by EPTC and other thiocarbamate herbicides is considered to result from an R-25788-mediated increase in the rate of EPTC sulphoxidation followed by conjugation of EPTC-sulphoxide with glutathione [III. 2(ii), Scheme 9]. In maize, but not in oats, the R-25788 antidote increases the glutathione content and increases the glutathione *S*-transferase activity, and thus provides both the cofactor and the enzyme for the increased metabolism and detoxification of more EPTC-sulphoxide (Lay, Hubbell & Casida, 1975; Lay & Casida, 1976). Thus, R-25788 acts by specifically stimulating the synthesis of glutathione and glutathione *S*-transferase in the plant itself, and the fact that, the difference in root glutathione *S*-transferase activity between R-25788-treated plants and the controls is retained on enzyme purification, implies that increased enzyme activity resulted from modification of the protein components, and not from the presence of a low molecular-weight activator in antidote-treated plants or an inhibitor in the controls (Lay & Casida, 1976). The mechanism by which R-25788 interferes with the biochemistry of maize seedlings has no counterpart in mammals.

Antidotal activity of R-25788 extends to various herbicides (Stephenson & Chang, 1978; Stephenson, Ali & Ashton, 1983) many of which are metabolized by conjugation with glutathione and, in these cases, an increased glutathione content may implicate increased activity of glutathione *S*-transferase.

Thus, R-25788 serves as an inducer for maize glutathione *S*-transferase, but this explanation does not apply to structurally similar compounds to the thiocarbamate herbicides, which may act by analogue blockade (Stephenson & Chang, 1978).

They way in which an inducer temporarily alters the biochemistry of the plants concerned would seem to involve modification of the protein components of the enzyme in question, possibly by reaction with a herbicide intermediate, since enhanced enzyme

activity is retained on purification by sedimentation, electrolyte fractionation and column chromatography. Such change(s) to the enzyme protein components would seem to be entirely consistent with the change in enzyme activity that has been found. There is no likelihood of a matching change in gene expression, as this change in enzyme activity is not heritable and would best be regarded as a case of hypertrophy.

(4) *Intraspecies differential tolerance to herbicides*

The possible occurrence of differential resistance to herbicides amongst crop-plant cultivators and weed biotypes would seem to follow from the genetic control of herbicide detoxification through metabolism, and early trends seemed to support this supposition. Thus the resistance of *Cirsium arvense* ecotypes to 2,4-D reflected inherent physiological differences (Hodgson, 1970). A strain of *Lotus corniculatus* was developed by recurrent selection, which was resistant to 2,4-D homologues and 2,4,5-T (Devine *et al.*, 1975). Treatment of the emergent seedlings of strains of carrot, resistant and susceptible to 2,4-D, 2,4-DB and MCPB, produced a differential response; resistance in the resistant strain seedlings developed at some time between germination and the cotyledon stage of growth (Whitehead and Switzer, 1963). Again, in *Cirsium arvense* ecotypes, the more resistant varieties metabolized amitrole more rapidly than the more susceptible ones (Smith, Bayer & Foy, 1968).

The initial premise (*q.v.*) was strongly supported by the discovery:

(i) of a rice mutant, deficit of the relevant aryl acylamidase and susceptible to propanil (Matsunaka, 1972);

(ii) of a maize inbred GT112 mutant, which is susceptible to atrazine, and which is deficient in the glutathione *S*-transferase (Grogan, Eastin & Palmer, 1963; Eastin, Palmer & Grogan, 1964; Shimabukuro *et al.*, 1971) that is linked to a single recessive gene (Grogan *et al.*, 1963);

(iii) of a chloro-*sym*-triazine-susceptible maize mutant, which lacks the benzoxazinone derivatives responsible for the hydrolysis of the chloro-*sym*-triazine herbicides (Hamilton, 1964*a*).

Several crop cultivars and weed biotypes have been found, which are resistant to herbicides.

Thus, for example, the differential metabolism of chloramben methyl ester [Section III. 2(ii)] has been proposed as a physiological basis to account for the resistance and susceptibility of four cucumber lines to this herbicide (Miller, Penner & Baker, 1973). Investigation of the genetic basis for the difference between these resistant and susceptible lines showed that although gene action is primarily additive, partial dominance of the genes controlling resistance occurs (Miller, Baker & Penner, 1973).

The main metabolic pathway for diuron metabolism both in resistant and susceptible sugar-cane cultivars appears to be by *N*-demethylation and glycosidation (Scheme 5). Metabolism was faster in the resistant cultivar than in the susceptible one (Liu, Shimabukuro & Nalewaja, 1978), and this apparently accounts for the tolerance of sugar-cane varieties to diuron (Osgood, Romanowski & Hilton, 1972).

In the case of the crop cultivars of soyabean (Smith & Wilkinson, 1974; Mangeot, Slife & Rieck, 1979) and tomato (Stephenson, McLeod & Phatak, 1976), resistance to metribuzin was also attributed to differences in the rates of herbicide metabolism (Scheme 6). But, Oswald, Smith & Phillips (1978) have found, in work with cell

suspensions of soyabeans, that metribuzin metabolism was inoperative in the case of the susceptible cultivars, due to the accumulation of a low molecular-weight inhibitor for the enzyme responsible for metribuzin metabolism and detoxification. Resistant cultures metabolized the inhibitor into an ineffectual form. Thus, at any rate in soyabean plants, selectivity seems to be determined by the accessibility of the inhibitor to the enzyme concerned with resistance.

Sagaral & Foy (1982) found a maize TXS114 cultivar that was highly resistant to EPTC both in the presence and absence of antidote protection, and most of the EPTC-susceptible cultivars showed significant improvement, when R-25788 was used in combination with EPTC, but R-25788 did not alleviate EPTC toxicity towards the susceptible XL55 and XL379 cultivars.

Genetic differences in resistance to pyrazone have been shown amongst various sugar-beet lines, and a direct relationship has been established between the resistance of plants to pyrazone and the rate of pyrazone metabolism (Stephenson, Baker & Ries, 1971).

The discovery of various weed biotypes, tolerant to atrazine, was the first example of genetically induced tolerance to be recognized amongst naturally occurring plant species. Investigation of the mechanism in *Chenopodium album*, *Senecio vulgaris* and *Amaranthus blitoides* showed that the tolerance found is not concerned with differences in atrazine absorption, translocation or metabolism between tolerant and susceptible biotypes (Jensen & Stephenson, 1973; Jensen, Bandeen & Souza Machado, 1977; Jensen, Stephenson & Hunt, 1977; Gressel *et al.*, 1983), but may be associated with structural or conformational changes in chloroplast membranes, and this was confirmed by Arntzen, Ditto & Brewer (1979). There is a hint in this and allied investigations (Pfister & Arntzen, 1979; Fister, Radosevich & Arntzen, 1979) that the mode of action of herbicides as well as their absorption, translocation and metabolism may, in certain circumstances, contribute also to herbicide selectivity, and the case of dalapon (Section V) is important.

(5) *Improved resistance through genetic manipulation*

The possibility of introducing foreign genes for herbicide tolerance into crop plants, where the changed expression would improve selectivity, represents a spectacular advance in plant protection. Recent progress in molecular biology facilitates the transfer of genes which, for example, might encode an inhibited enzyme relating either to herbicide detoxification or to its mode of action. Both of these possibilities involve the network of plant biochemistry but, whereas the former would improve selectivity by increasing the rate of herbicide metabolism and detoxification, the latter would produce this effect by disturbing the biochemical mechanism of herbicide action. Thus, it is envisaged that it might be possible to impose enhanced selectivity on a given arable ecosystem through genetic interference in the crop plant with the mode of action of a selective or an unselective herbicide. But, the switching-on or -off of genes concerned with resistance to chemicals is evocative of a wider connotation, which has to do with the fundamental understanding of plant growth and development at the genetic level. Recent trends in the transfer of foreign genes, however, have been confined so far to general cases, and the scope for expansion to other crop plants, especially to monocotyledons, presents considerable difficulty.

Thus, Comai *et al.*, (1958) introduced a mutant allele to the gene that encodes an enzyme (EPSP synthase), less sensitive to glyphosate, into tobacco plants. Expression of this gene enhanced tolerance to this herbicide in the transformed plants.

It ought to be explained that 3-phosphoshikimate 1-carboxyvinyl-transferase (EPSP synthase) is considered to be the target of glyphosate in plants, and that EPSP synthase catalyses the formation of 5-enol-pyruvylshikimate 3-phosphate from either phosphoenolpyruvate or shikimate 3-phosphate. The inhibition of this step in the shikimic acid-pentose shunt blocks aromatic amino-acid production, causes the accumulation of shikimate, and leads eventually to cell death (Steinruecken & Amrhein, 1980; Amrhein *et al.*, 1980). Comai, Sen & Stalker (1983*b*) considered that tolerance would result from the presence of a modified enzyme and in effect Comai *et al.* (1985) tested whether the expression in plants of a gene encoding glyphosate-resistant EPSP synthase conferred herbicide tolerance.

These workers (Comai *et al.*, 1985) used:

(i) a mutant allele of the aroA locus of *S. typhimurium* (Comai *et al.*, 1983*b*) encoding an EPSP synthase in which the single substitution of a proline for serine residue diminished the affinity for glyphosate (Stalker, Hiatt & Comai, 1985) without impairing enzyme efficacy:

(ii) a T-DNA-based vector, which is transmitted to plant cells on infection with *Agrobacterium tumefaciens*, and which is integrated with the plant-cell DNA. The segment in question carries genes, which have been expressed in the plant cell, and the aroA gene of *Salmonella* has been isolated and sequenced (Stalker *et al.* 1985).

In constructs, made from this gene, transcriptional signals were taken from octopine synthetase gene (ocs) or the tml polyadenylation signal was used. These constructs were cloned. For insertion of ocs-aroA and mas-aroA into the plant genome, co-integrate plasmids were generated by recombination of pPMG55 and pPMG85 and pRiA4 (Comai *et al.*, 1983*a*, *b*). One of these co-integrate plasmids contained up to ten copies of pPMG55 tandemly arranged in the T-L-DNA, and another co-integrate contained one copy of pPMG85; the strains containing these plasmids were selected for plant transformation. There followed (Comai *et al.*, 1985) the identification of transformed plants, co-cultivation, and the investigation of whether the mRNAs were properly translated and whether the mutant bacterial aroA gene would confer tolerance on tobacco plants.

A great deal of work showed that expression in tobacco plants of a glyphosate-resistant EPSP synthase from *S. typhimurium* conferred tolerance to glyphosate, where the degree of tolerance depended on the expression level of aroA-encoded EPSP synthase. Hence, in effect, Comai *et al.* (1985) had shown that a plant metabolic enzyme and its bacterial counterpart were complementary.

The problem of improved resistance to *sym*-triazine herbicides, which kill plants by interference with electron transfer in photosynthesis, is currently being tackled using the photo-affinity label, azido-atrazine for recognition of the herbicide-binding site (in the chloroplast thylakoids) (Grierson & Covey, 1984). The receptor is considered to be the protein (mol. wt. 3200) product of photogene 32, and is encoded by the plastome. In fact, many weed species have developed resistance to *sym*-triazines (III. 4) and, in one case (Beversdorf, Weiss-Lerman & Erickson, 1980), this has been correlated with misincorporation of a single base in photogene 32, which in turn resulted in a single

change from serine to glycine in the encoded protein sequence. Conventional breeding between *Brassica rapa*, which is resistant to the *sym*-triazines and the more susceptible oil-seed rape (*Brassica napus*) has led to the development of resistant crop plants (Beversdorf *et al.*, 1980), and attempts are now being made (Grierson & Covey, 1984) to transfer resistance to *sym*-triazines from *Solanum nigrum* to potato plants by means of protoplast fusion. The success of this work would seem to depend on successive breeding from the transformed crop plants, and in the case of potatoes, *Solanum nigrum* is considered to be pretty poisonous.

(6) *Contribution to herbicide design from differential plant–enzyme activities*

An initial finding by Synerholm & Zimmerman (1957) that 2,4-dichlorophenoxyalkanoic acids, which have a side-chain with an even number of *C* atoms such as the butyric, caproic and caprylic acids, although inactive *per se* showed growth-regulator activity in higher plants through their biotransformation into the acetic homologue 2,4-D, was brilliantly extended by Wain *et al.*, who synthesized hundreds of structurally related compounds, developed sensitive methods of botanical screening and investigated relevant species differences in plant–enzyme activity (*inter alios* Fawcett, Ingram & Wain, 1954; Wain & Wightman, 1954; Fawcett *et al.*, 1959).

Thus, the low capacity of pea and tomato tissues for β-oxidation was considered to be consistent with tolerance to 2,4,5-TB and, similarly, celery and clover tissues, which were unable to oxidize 2,4-DB, were found to be resistant to this herbicide. In legumes, oxidative degradation of 2,5-dichlorophenoxybutyric acid was arrested by formation of the β-hydroxy derivative (Fawcett *et al.*, 1959) but, in wheat, the reaction sequence leading to the corresponding acetic acid was complete. Accordingly, tolerance in legumes, for example, to 2,4-DB was attributed (Wain, 1954, 1955*a*, *b*, 1957) to a low enzymic complement for β-oxidation of the aliphatic side-chain.

Wain (1955*a*, *b*), Shaw & Gentner (1957) and Matsunaka (1972) have reported susceptible weeds (*Amaranthus* species, *Chenopodium album*, *Cirsium arvense*, *Fumarium* species, *Sinapis arvensis* and *Urtica urens*) to 2,4-DB, MCPB and 2,4,5-TB and resistant crop plants (alfalfa, carrot, celery, flax [and linseed] and parsnip) to 2,4-DB and MCPB and (*Brassica* species, flax [and linseed], *Meliototus* species and soyabean) to 2,4,5-TB. A great deal of work by the team at Wye College (*q.v.*) led to the eventual development of 2,4-DB. MCPB and 2,4,5-TB as commercial herbicides. Tests showed that 2,4-DB and MCPB were good selective weed killers, which were not themselves phytotoxic, but which were converted into active herbicides in plants, and consequently their actions were relatively slow. MCPB can be used in cereals without injuring the young crop plants, and can be used safely in clover, although it damages peas. 2,4-DB is used for weed control in alfalfa.

Later workers (Linscott, Hagin & Dawson, 1968; Linscott & Hagin, 1970) showed that in legumes 2,4-DB metabolism involved a side-chain lengthening process to afford 2,4-dichlorophenoxyalkanoic acids with a side-chain containing six (caproic acid) or ten (decanoic acid) carbon atoms. These workers considered the resistance of legumes to 2,4-DB to be due to the dominance of the side-chain lengthening process over the competitive β-oxidation, which occurs both in resistant and in susceptible species, thereby preventing the production of a lethal dose of 2,4-D in resistant species. Furthermore, 2,4-DB has been found to be rapidly ring hydroxylated and conjugated

with glucose or amino acids in white clover (*Trifolium repens*) cell suspensions (Smith, 1979), and Smith & Oswald (1979) have attributed the inherent tolerance of legumes to 2,4-DB to be due in part to the preferential rate of ring hydroxylation and conjugation in those species. It is also feasible that a lower rate of absorption of 2,4-DB and a more rapid rate for the detoxification of the resulting 2,4-D may contribute to the tolerance of legumes (amongst others Hauf & Behrens, 1974). Whilst these later observations do not mitigate against the monumental contribution of Wain *et al.*, (*q.v.*), they suggest that the biochemistry of legumes may be more complex than had previously been suspected.

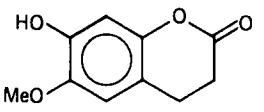
Another way in which established species differences in the activity of plant enzymes involved with herbicide metabolism may contribute to herbicide design is through the incorporation of the transformable groups of the corresponding enzyme substrates into herbicidally active substances. Such incorporation would transfer a degree of selectivity, commensurate with the difference in plant–enzyme activity that had been found. Whilst the literature does not reveal the extent of this approach, there is, for example, an available background of information on glycosidation by plants, which is relevant to potentially glycosylatable candidate compounds. Thus, for example, the *O*-glucosidation of maleic hydrazide in tobacco, but not in *Stellaria* species is predictable and, in the case of compounds like chloramben, *N*-glycosidation would protect the sugar-beet, whereas *Stellaria* species would be susceptible to herbicide, regenerated from the ester glucoside.

IV. ALLELOPATHIC AGENTS AS REPLACEMENT HERBICIDES

There is a bewildering mass of information on the apparent allelopathic effect of weeds on crop plants and vice versa (Rice, 1984) and in many exercises where allelopathy is said to be implicated little attempt has been made to take account of the effect of competition between the species and of climactic factors. The data *inter alia* on *Agropyron repens* in wheat, *Chenopodium album* in sugar-beet, *Cirsium arvense* in beans and clover, *Echinochloa crus-galli* in rice, *Setaria faberii* in soyabeans and *Sorghum halepense* in cotton and sugar-cane, however, imply that in these cases real allelopathic principles were involved. Work on the allelopathic influence of crop plants on weeds is generally unimpressive and, had the production and release of effective allelopathic agents by crop plants been widespread, the need for commercial herbicides would not have occurred. Nevertheless, Fay & Duke (1977) appear to have demonstrated a genuine allelopathic effect against *Brassica kaber* variety *pinnatifida* with the germplasm of selected accessions of oats plants, which have a high scopoletin (55) content. [Compound (55) had been identified previously in oats roots (Goodwin & Kavanagh, 1949; Martin, 1957)]. In co-cultures the growth of *Brassica kaber* was diminished significantly; individual plants suffering severe chlorosis, stunting and twisting (Fay & Duke, 1977).

Much more work needs to be done on the genetics of allelopathic agents and many more screening programmes need to be made before breeding can be undertaken to produce viable cultivars of crop plants, which are allelopathic to specific weeds.

The residues of allelopathic crop plants and weeds have been used for the partial weed control of crops. Thus, the application of mulches of sorghum and sudan grass to apple orchards, in spring, reduced weed growth respectively by 90 and 85 % without harming



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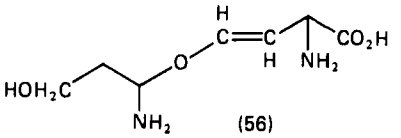

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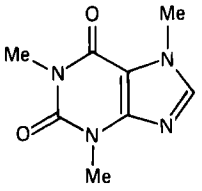
Formulae 56

the trees, and in a three-year field trial, the populations of *Digitaria ischaeum* (monocotyledon) and *Portulaca oleracea* (dicotyledon) were reduced respectively by 98 and 70% (Putnam & De Frank, 1979, 1983). Basically, this experience demonstrated the successful transference of unidentified allelopathic principles to a relevant ecosystem.

More to the point, allelopathic principles, isolated from various sources, have been applied as herbicides, Thus, a useful allelopathic agent rhizobitoxine, 2-amino-4-(2-amino-3-hydroxypropoxy)*trans*-but-3-enoic acid (56), is produced by *Rhizobium japonicum* in soyabean nodules (Owens, Thompson & Fennessey, 1972) and causes the host plant to become chlorotic. Compounds (56) irreversibly inactivates β-cystathionase, and thus inhibits the biotransformation of methionine into ethylene. If compound (56) was used at a dosage as low as 3 oz/acre, it was an efficient herbicide (Anonymous, 1969). Dose-wise, compound (56) behaved similarly to amitrole in post-emergence tests. *Digitaria sanguinalis* was moderately susceptible to (56) whereas Kentucky bluegrass was very resistant (Owens, 1973), so that compound (56) might be useful for the control of *Digitaria* in bluegrass lawns. On the other hand, amitrole is phytotoxic both to bluegrass and to *Digitaria*.

Agrostemmin, an allelopathic agent from *Agrostemma githago* decreased the incidence of forbs in pastures, treated at a dose level of 1·2 g/ha, and increased both the yield and the *N* content of the grass, (Gajic, 1973).

For an allelopathic principle to be useful for vegetable production, however, it must kill dicotyledons selectively and in this connection experience is limited to the utilization of caffeine (57) and its *N*-demethylation products, theophylline (58) and parxanthine (59) from the coffee tree (*Coffea arabica*) (Chou & Waller, 1980*a*, *b*). Rizir, Mukerji & Mathur (1981) found that caffeine, isolated from the methylene dichloride fraction of *Coffea arabica* seeds, completely inhibited the germination of *Amaranthus spinosus* (dicotyledon) seeds at a dosage of 1200 μg/ml in laboratory tests, whereas crop plant seedlings, like black gram (*Phaseolus mungo* [*Vigna mungo*]) were unharmed. Compound (57) also inhibited germination of seven other dicotyledonous weed species. Thus, caffeine shows considerable promise as a selective herbicide, at any rate in certain crops. It is feasible that caffeine acts (*q.v.*) by blocking the ready elaboration of purine bases into the complex cofactors, essential for the germination and growth of the weed species (Hathway, 1986, unpublished observations).



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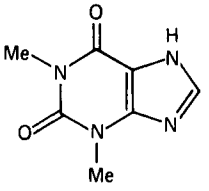

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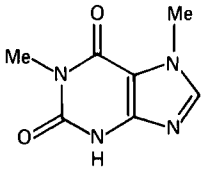

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V. HERBICIDES, WHICH CONFLICT WITH THE FUNDAMENTALS OF SELECTIVITY

The principles of selectivity, which have been developed in this article, do not appear to apply in the case of a few common herbicides.

Thus, in respect of the modest degree of selectivity shown by dalapon, investigation eliminated any possible contribution from differential uptake, translocation and metabolism, with a result that species differences in the mode of action (see sub-section III. 4) were explored (Foy, 1961*a*). Pyruvate metabolism is central to plant biochemistry, and quite irrespective of the mechanism concerned (Foy, 1961*b*; Leasure, 1964), if dalapon interrupts pyruvate metabolism, it must compete either with β-alanine or with pantoic acid. It might be assumed that pantothenic acid biosynthesis would then be disrupted and functional supplies of coenzyme A would be impaired. In plants, coenzyme A modulates pyruvate oxidation, citrate synthesis and α-oxoglutarate oxidation in the citric acid cycle, fatty acid and steroid biosynthesis and catabolism as well as auxin action, and through its control of energy transfer, it also influences carbohydrate, lipid and *N* metabolism. Accordingly, it is crucial to plant biochemistry and growth, and any interference with citric acid cycling would disturb related metabolic processes, such as *N* metabolism. In this connection, the dark green appearance of dalapon treated plants, their delayed maturation and the prolongation of vegetative growth are characteristic of plants with an unusually rich supply of available *N*. It is reasonable to suppose that dalapon may act at more than one site, and thus would compete with say pyruvate, β-alanine and pantoic acid to a variable extent in different plant systems. Synthesis in the shoots clearly requires the products of photosynthesis, and if the process were disturbed, the meristematic regions would be the first to suffer from the deficiency. Alternatively, work by Prasad & Blackman (1964) showed that dalapon caused abnormality to the roots, which would imply an indirect involvement with light, which was consistent with other evidence. Accordingly, the low degree of dalapon selectivity towards cotton and sorghum would appear to relate to a differential response of plant biochemistry, at the tissue level, to dalapon or a dalapon metabolite.

Other herbicides, however, have been found to be unselective. Thus, in the case of the bipyridiniums, diquat is used (i) for aquatic weed control; (ii) for pre-harvest desiccation of oil-seed crops, and (iii) for potato-haulm desiccation (Brian, 1966; Headford & Douglas, 1967), and paraquat (i) for rapid knock-down of vegetation; (ii) for the control of *Imperata cylindrica*, *Papsalum conjugatum* and *Panicum nodosum* (monocotyledons) and *Eupatorium oderatum* and *Melastroma malabathricum* (dicotyledons) in plantation crops (Jeater, 1964); (iii) for total destruction of swards in pasture renovation (Douglas, Lewis & McIlvenny, 1965), and (iv) in the drillings of cereals and kale into treated sward without ploughing (Hood, 1965; Hood, Jameson & Cotterell, 1963). None of these uses implicates selectivity and, in fact, the bipyridiniums act ubiquitously throughout higher plants (Homer *et al.*, 1960; Mees, 1960). The rapidity of foliar uptake, a capacity to kill perennial weeds at low dosage and the non-transference of herbicidal action via the soil are the properties, which have been exploited to afford mechanical selectivity.

Unlike the bypyridiniums, glyphosate is a systemic non-selective herbicide which is translocated by symplastic transport to the young growing points of the plants that it enters (Grossbard *et al.*, 1984). The mode of action of glyphosate is mentioned in Section III. 5.

Monuron and amitrole are also unselective. Monuron is used for total weed control. Amitrole is used for weed control in apple and pear orchards and for weed treatment prior to planting kale (*Brassica oleracea*), maize, oil-seed rape, potatoes and wheat (Knöller, 1966; Carter, 1975).

VI. SUMMARY

1. Morphological and physico-chemical barriers, which limit herbicide entry into a plant facilitate resistance to toxicity, and any intraspecies differential contributes to herbicide selectivity. Differential translocation, complicated by symplastic or apoplastic transport, possible leakage of herbicide from phloem to xylem, the binding of herbicide to cell-wall components and its capacity to inflict contact injury, also contributes to herbicide selectivity. If herbicide uptake, translocation and metabolism in plants be represented by a linear model, differences in the rate processes occurring in the various compartments parallel herbicide selectivity, and metabolism is seen to play a major role.

2. Where progenitor of biologically active material is administered to plants, the susceptible species must have high activity of enzymes responsible for bioactivation. The fact that auxin, resulting from indolylacetonitrilase activation of the 3-indolylacetonitrile precursor, stimulates the growth of cereal but not leguminous plants is consistent with the isolation of indolylacetonitrilase from barley seedlings. Diclofop-methyl herbicide is activated by high carboxylesterase activity in *Avena fatua*, but not in wheat and sugar-beet. On the other hand, high activity of herbicide-metabolizing enzymes associated with detoxification confers resistance, where active herbicide is administered, and 2,4-D is transformed by 2,4-D *p*-hydroxylase in cereal crops, but not in the encroaching dicotyledonous weeds, into inactive ring-hydroxylated analogues, so that 2,4-D growth-regulating activity is lost from the shoots and roots of the crop plants.

3. Species differences in the uniquely important metabolism of herbicides coincide with and account for the differential resistance/susceptibility observed. The relevance

of mixed-function oxydases, reminiscent of those in mammals (Hathway, 1970–81), is stressed by recent isolation (i) of a cotton *N*-demethylase responsible for *N*-demethylation of monuron and diuron; (ii) of the 2,4-D *p*-hydroxylase from cucumber and pea plants and (iii) of a sugar-beet metamitron deaminase, and the use of crude enzyme preparations to hydroxylate pyrazone (Keller, Eberspacher & Linger, 1979) and to *N*-dealkylate dinitroaniline herbicides. It is highly probable that the ring hydroxylation of (dicamba, chlorpropham, perfluidone and propham, the substituted urea herbicides, and bentazone), deamination (of metamitron and metribuzin), *O*-demethylation (of metoxuron), *N*-dealkylation (of substituted urea herbicides, *sym*-triazines, dinitroanilines and possibly EPTC) and sulphoxidation (of EPTC) in plants are mediated by the mixed-function oxydases, present. The importance of other herbicide biotransformation in plants is stressed by recent isolation of the carboxylesterase responsible for diclofopmethyl hydrolysis, of the aryl acylamidase concerned with propanil hydrolysis, of the triazinyl glutathione *S*-transferase relating to 2-chloro-*sym*-triazine conjugation, and of the aryl glutathione *S*-transferase concerned with the fission of the diphenyl ether bridge in fluordifen. In addition, glycosidation of herbicides and their ring hydroxylated metabolites is widespread (see for example the biosynthesis of metribuzin N-β-D-glucoside involving UDP-glucose : metribuzin-*N*-glucosyl transferase).

4. Metabolic regulation is imposed on the action of herbicides and their fate in plants through genetic control of the rate of enzyme synthesis. The enzymes concerned appear to be constitutive, as they are present in the microsomal fractions of the various tissues in approximately constant amounts, irrespective of herbicide exposure.

5. The fact that the activity of 2,4-D *p*-hydroxylase, *trans*-cinnamic hydroxylase and cytochrome *P*-450 have been stimulated by treatment of the plants with specific herbicides is reminiscent of the induction of mono-oxygenases in mammals. Furthermore, R-25788-stimulated synthesis of EPTC glutathione *S*-transferase and glutathione in maize plants is the basis of R-25788 antidotal protection. The disturbances in plant biochemistry caused by induction are temporary, and they are not heritable.

6. Genetic control of herbicide metabolism is substantiated by the differential resistance to herbicides shown by crop-plant cultivars and weed biotypes. Thus, genetic difference in resistance to pyrazone occurs amongst various lines of sugar-beet, and the resistance of the plants and the rate of pyrazone metabolism are directly correlatable. It is noteworthy (i) that a rice mutant, deficit of the aryl acylamidase, has been found, which is susceptible to propanil, and (ii) that a maize inbred mutant, which is deficient in glutathione *S*-transferase activity, is susceptible to atrazine. In soyabean cultivars, however, susceptibility to metribuzin involves a low molecular-weight inhibitor, which blocks herbicide metabolism.

7. The introduction of foreign genes for herbicide tolerance into crop plants, thereby improving resistance in the transformed plants, strongly supports the dependence of selectivity on plant biochemistry as it relates to herbicides. Whilst recent trends have been limited to general cases, present data are impressive, and (i) the expression in tobacco plants of a glyphosate-resistant EPSP synthase from *Salmonella typhimurium* conferred tolerance to glyphosphate in the transformed plants. (ii) Some weed species have developed resistance to *sym*-triazines and, in one case, this has been correlated with misincorporation of a single base in photogene 32, which in turn caused a single change

from serine to glycine in the encoded protein. Conventional breeding between *Brassica rapa*, which is resistant to *sym*-triazines, and the more susceptible oil-seed rape (*Brassica napus*) effected the development of resistant crop plants.

8. Some information has been assembled, which suggests that data on species differences in plant–enzyme activities may assist in the modelling of new herbicides.

9. The possible use of allelopathic principles from various sources as replacement-herbicides is relevant, and the application of caffeine from *Coffea arabica* seeds to a black gram (*Phaseolus mungo*) crop completely inhibited the germination of *Amaranthus spinosus* and seven other dicotyledonous weed species, leaving the crop-plant seedlings unharmed. A mechanism is suggested.

10. In the case of dalapon, the mode of action disturbs the plant biochemistry. This factor is genetically controlled, and a modest selectivity depends on the varying extent to which this occurs in the different species. But, still other herbicides (bipyridiniums, glyphosate, amitrole and monuron) are simply unselective.

11. In essence, the auto-defence mechanism of plants against chemical attack has been explored in this article, and the possibility of gene transfer for herbicide tolerance, of which two cases have now been established, reveals another dimension.

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