concern in eggs and meat of laying hens.

ACKNOWLEDGMENT

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Registry No. FEN, 51630-58-1; 4'-OH-FEN, 67882-25-1; (±)-*cis*-3-CH_2OH-2-Cl-BA lactone, 117606-18-5; (±)-*trans*-3-CH_2OH-2-Cl-BA lactone, 117606-19-6; 3-COOH-2-Cl-BA (isomer 1), 117606-20-9; 3-COOH-2-Cl-BA (isomer 2), 117606-21-0; 2-OH-2-Cl-BA, 97635-01-3; 3-CH_2OH-2-Cl-BA (isomer 1), 97634-99-6; 3-CH_2OH-2-Cl-BA (isomer 2), 97635-00-2; 2-OH-3-CH_2OH-2-Cl-BA, 72041-48-6.

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Structure–Activity Studies of Tetrazole Urea Herbicides

Patrick Camilleri,* Michael W. Kerr, Terence W. Newton, and John R. Bowyer

The Hill inhibition activity of a novel class of (heteroaryloxy)urea derivatives has been found to be related to the partitioning characteristics of these compounds, as measured by their 1-octanol/water partition coefficient (P). A parabolic relationship between pI_{50} and log P revealed that optimum in vitro activity is exhibited by compounds that have a log P approaching 4. This result contrasts with the herbicidal activity shown by these phenylureas. No clear relationship exists between log P and herbicidal activity. However, the most phytotoxic (heteroaryloxy)urea has log $P \approx 2$, a value significantly lower than those reported for some of the most successful photosynthetic herbicides.

Of the amide-type herbicides (acylanilides, phenylureas, biurets, *N*-phenylcarbamates, uracils) the phenylurea group has been of particular interest in connection with its relationship to photosystem II (PS II) inhibition. A number of structure–activity relationships (SAR) in the literature (Hansch, 1969; Seewald et al., 1978; van den Berg and Tipker, 1982; Kakkis et al., 1984; Takemoto et al., 1984; Mitsutake et al., 1986; Camilleri et al., 1987) have shown that hydrophobic, electronic, and steric factors are the physicochemical parameters that define the ability of this class of molecules to inhibit the Hill reaction. Al-

Sittingbourne Research Centre, Shell Research Limited, Sittingbourne, Kent ME9 8AG, U.K. (P.C., M.W.K., T.W.N.), and Department of Biochemistry, Royal Holloway and Bedford New College, Egham Hill, Egham, Surrey, TW20 0EX, U.K. (J.R.B.).

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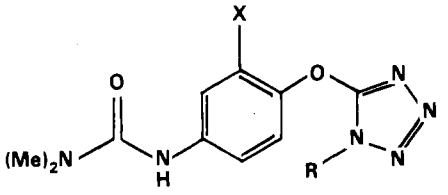
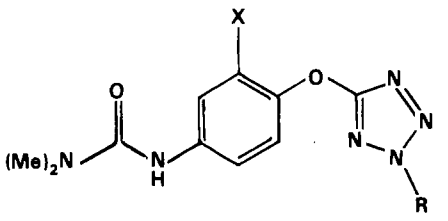
though simple phenylureas, e.g., diuron and isoproturon, have been known for some time to be excellent Hill inhibitors (Wessels and van der Veen, 1956; Bishop, 1958; Hansch, 1969), it has been shown recently (van den Berg and Tipker, 1982; Kakkis et al., 1984; Camilleri et al., 1987) that other phenylureas with "bulkier" groups in the meta and para positions to the urea moiety are also potent inhibitors; some of these molecules cause 50% inhibition of the Hill reaction at a concentration as low as 10^{-8} M.

This report describes the analysis of the quantitative structure–activity relationships of a novel class of "bulky" phenylureas of general structures I and II, which contain a tetrazole moiety, substituted either in the 1- (type I) or the 2-position (type II). R is a substituted alkyl group whereas X on the phenyl ring is either a hydrogen or a chlorine atom.



(I)



(II)

The hydrophobicity of the molecules has been described in terms of the logarithm of their 1-octanol/water partition coefficient (log P). In cases where log P values were not measured experimentally by the "shake-flask" method, they were calculated from retention data obtained from high-pressure liquid chromatography (HPLC). For compounds where R is a phenyl group, the hydrophobic parameter π of the substituents on the phenyl group was related to the Hill inhibition activity of the corresponding molecules. Steric parameters have been defined in terms of the STERIMOL length L (Verloop et al., 1976).

The structure–activity profiles obtained for this novel class of phenylureas strongly suggest that the binding of the ureas at the PS II site (possibly the receptor site for the secondary acceptor plastoquinone, Q_B (van Rensen, 1982)) depends primarily on the hydrophobic nature of these molecules.

EXPERIMENTAL SECTION

Phenylureas. All phenylureas were synthesized by the Organic Chemistry Division of Sittingbourne Research Centre and were used without further purification.

Hill Inhibition Assay. Compounds were assayed for their potency to inhibit the Hill reaction, as measured by pI_{50} values determined on isolated pea thylakoids. The procedure detailed by us in a previous report (Camilleri et al., 1987) was followed.

Partition Coefficients. The 1-octanol/water partition coefficients (P) of a selected number of type I and type II tetrazole phenylureas were measured by the shake-flask method. The compound concentrations in both the octanol and water phases were analyzed by absorption measurements at 245 nm. The partition coefficients determined by the shake-flask method are listed in Tables I and II,

Table I. Hill Inhibitory Activity (pI_{50}) and log P Values of Type I Tetrazole Ureas

compd	R	X	pI_{50} obsd	pI_{50} calcd[a]	log RT	log P
1	t-C_4H_9	H	5.57	5.80	0.62	1.65
2	c-C_6H_{11}	H	6.09	6.19	0.73	2.18[b]
3	C_8H_{17}	H	7.00	6.99	1.04	3.96[b]
4	CH_2=$CHCH_2$–	H	5.19	5.21	0.56	1.00
5	$-CH_2C_6H_5$	H	6.00	5.84	0.62	1.70
6	$-CH_2CO_2C_2H_5$	H	4.74	4.91	0.55	0.70[b]
7	CH≡CCH_2–	H	5.47	5.21	0.56	1.00
8	C_2H_5	Cl	5.73	5.67	0.60	1.50[b]
9	t-C_4H_9	Cl	6.28	6.24	0.71	2.25

[a] Calculated by eq 1. [b] Measured by shake-flask method.

Table II. Hill Inhibitory Activity (pI_{50}) and log P Values of Type II Tetrazole Ureas

compd	R	X	pI_{50} obsd	pI_{50} calcd[a]	log RT	log P
10	CH_3	H	5.29	5.12	0.52	0.63[b]
11	C_2H_5	H	5.94	5.68	0.56	1.10[b]
12	i-C_3H_7	H	6.11	6.03	0.61	1.45
13	t-C_4H_9	H	6.44	6.55	0.67	2.08[b]
14	c-C_6H_{11}	H	6.83	6.88	0.80	2.67[b]
15	C_8H_{17}	H	7.05	7.04	1.12	4.40
16	CH_2=$CHCH_2$–	H	6.05	6.21	0.59	1.65
17	$-CH_2C_6H_5$	H	6.83	6.66	0.68	2.25
18	$-CH_2CO_2C_2H_5$	H	5.54	5.70	0.59	1.12[b]
19	CH≡CCH_2–	H	6.10	6.21	0.61	1.65
20	$-CH_2CH_2CN$	H	4.49	4.65	0.51	0.28[b]
21	C_2H_5	Cl	6.31	6.26	0.63	1.70

[a] Calculated by eq 2. [b] Measured by shake-flask method.

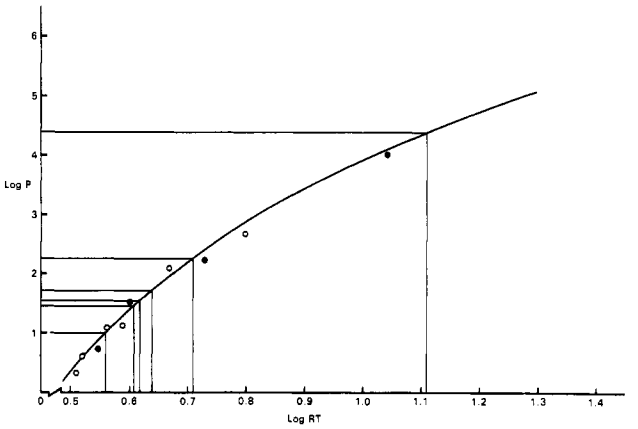


Figure 1. log P versus log RT for type I (●) and type II (○) tetrazole ureas.

which also include the partition coefficients determined indirectly for the rest of the compounds by an HPLC retention time method.

In the HPLC method a C-18 reversed-phase column (Spherisorb ODS2), 150 mm in length, was used. All compounds in Table I were eluted by a mixture of water and acetonitrile (2 + 3, v/v) flowing at a rate of 0.5 mL min^{-1} and were monitored at a wavelength of 245 nm. Figure 1 shows the relationship between the experimentally determined log P (using the shake-flask method) and the corresponding logarithm of retention time (RT). We have used this relationship to estimate the log P values of the remaining compounds in Table I from retention time measurements. An interesting feature of Figure 1 is that both type I and type II tetrazole phenylureas show related behavior on a C-18 column. In general type I compounds have higher log P values and longer retention times than the corresponding type II compounds.

RESULTS AND DISCUSSION

The measured pI_{50} values (where I_{50} is the molar concentration of inhibitor causing 50% inhibition in the Hill reaction) used in our structure–activity analysis are listed in Table I. These in vitro data and the corresponding octanol/water partition coefficients are related by eq 1 and 2 for type I and type II molecules, respectively.

$$pI_{50} = \underset{(0.56)}{1.25}\log P - \underset{(0.11)}{0.13}(\log P)^2 + \underset{(0.56)}{4.10} \quad (1)$$

$$n = 9,\ r = 0.96,\ s = 0.18$$

$$pI_{50} = \underset{(0.30)}{1.54}\log P - \underset{(0.06)}{0.21}(\log P)^2 + \underset{(0.32)}{4.23} \quad (2)$$

$$n = 12,\ r = 0.98,\ s = 0.16$$

In these equations the figures in parentheses are 95% confidence limits, n is the number of compounds considered, r is the correlation coefficient, and s is the standard deviation. Equations 1 and 2 predict optimal log P values of 4.8 and 3.7 for type I and type II compounds, respectively. However, since the data do not include compounds of log P greater than these "optimum values", the error on these numbers is large.

The coefficients and intercepts in the above equations are very similar, suggesting that both type I and type II tetrazole ureas interact with the same site of action on PS II. Moreover, it appears that such an interaction depends only on the lipophilic nature of the molecules and is independent of stereoelectronic contributions, mainly from the R group. The lack of a relationship between Hill inhibition and the size of R possibly reveals that the phenyl ring and the tetrazole moiety are out of plane with respect to each other, thus minimizing any steric interaction between R and substituents on the phenyl ring.

The substituent X on the phenyl ring again appears to influence activity solely by its contribution to the lipophilicity of the tetrazole urea as a whole. However, the importance of an electronic effect from this functional group cannot be fully assessed as the number of compounds that have been analyzed with X substituents is too low.

Equations 3–5 summarize the structure–activity studies reported in the literature for other classes of phenylureas. (a) 1-Phenyl-3,3-dimethylureas, $XC_6H_4NHCON(CH_3)_2$ (Hansch, 1969):

$$pI_{50} = \underset{(0.49)}{1.08}\log P + \underset{(1.11)}{1.93}\sigma + \underset{(0.71)}{2.71} \quad (3)$$

$$n = 12,\ r = 0.93,\ s = 0.457$$

σ is the Hammett constant used to assess the electronic effect of substituents. (b) Phenoxyphenyl-3,3-dimethylureas, $XC_6H_4OC_6H_4NHCON(CH_3)_2$ (van den Berg and Tipker, 1982):

$$pI_{50} = \underset{(0.36)}{1.07}\log P - \underset{(0.71)}{1.18}\log(\beta 10^{\log P} + 1) + \underset{(1.0)}{3.20} \quad (4)$$

$$n = 14,\ r = 0.94,\ s = 0.246,\ \log\beta = 3.60$$

β is a constant used in the bilinear model. (c) Phenyl-3,3-dimethylureas, $XC_6H_4NHCON(CH_3)_2$ (Kakkis et al., 1984):

$$pI_{50} = \underset{(0.21)}{0.91}\log P - \underset{(0.58)}{1.08}\log(\beta 10^{\log P} + 1) - \underset{(0.07)}{0.12}BR + \underset{(0.48)}{3.77} \quad (5)$$

$$n = 17,\ r = 0.95,\ s = 0.414,\ \log\beta = -4.34$$

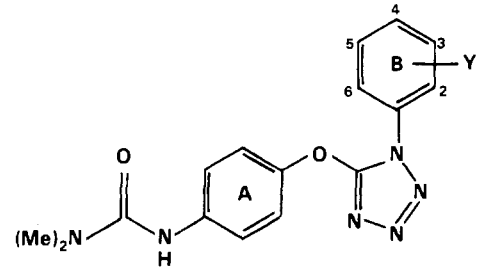
BR is a steric parameter. With the exception of eq 3, where electronic effects seem to make some contribution to Hill inhibition, the relationships confirm that, as with the tetrazole ureas, hydrophobicity largely determines the in vitro activity of these molecules. In fact the substituted phenyl moiety in these ureas can be summarized as hydrophobic, bulky, and sterically undemanding.

Table III. Hill Inhibition Activity (pI_{50}) and Physicochemical Parameters of Type III Tetrazole Ureas

				PI(50)			
compd	Y_2	Y_4	Y_5	obsd	calcd[a]	L	
22	F	H	CF_3	6.72	6.68	1.02	2.65
23	Cl	H	CF_3	6.77	6.72	1.59	3.52
24	H	H	NO_2	6.06	5.99	−0.28	2.06
25	H	Cl	CF_3	6.96	7.05	1.59	2.06
26	H	F	CF_3	6.75	6.82	1.02	2.06
27	H	NO_2	H	6.02	5.99	−0.28	2.06
28	H	NH_2	H	5.05	5.13	−1.23	2.06
29	H	H	SO_2CF_3	6.46	6.57	0.55	2.06
30	H	H	H	6.38	6.20	0	2.06
31	H	H	CF_3	6.89	6.75	0.88	2.06
32	H	CF_3	H	6.68	6.75	0.88	2.06
33	Cl	Cl	Cl	6.95	6.87	2.13	3.52
34	CF_3	H	H	6.30	6.47	0.88	3.30

[a] Calculated by eq 7.

In order to gather more information on the nature of the interaction of the tetrazole ureas with the receptor site, we have analyzed in vitro data for a number of tetrazole ureas of type III where the terminal phenyl group B is



(III)

substituted in the 2-, 4-, and 5-positions. Data are presented in Table III. For these compounds we found that the Hill inhibiting activity can be expressed in terms of the sum of the hydrophobicity constants of the substituents in the 2-, 4-, and 5-positions Y, that is $\sum\pi$, and the STERIMOL parameter L (Verloop et al., 1976) for a substituent in the 2-position. As the substituents in the latter position are spherically symmetrical, L is close to the diameter of these substituents.

The structure–activity relationships obtained for type III molecules are given in eq 6 and 7.

$$pI_{50} = \underset{(0.13)}{0.68}\pi - \underset{(0.09)}{0.17}\pi^2 + \underset{(0.12)}{6.21} \quad (6)$$

$$n = 13,\ r = 0.95,\ s = 0.12$$

$$pI_{50} = \underset{(0.14)}{0.72}\pi - \underset{(0.07)}{0.12}\pi^2 - \underset{(0.15)}{0.23}L + \underset{(0.32)}{6.67} \quad (7)$$

$$n = 13,\ r = 0.98,\ s = 0.12$$

Again, as in the case of type I and II compounds, the in vitro activity of type III molecules is largely determined by the hydrophobic nature of the substituent on the tetrazole ring. The steric parameter L only accounts for about 3% of the variance compared to 91% for the π and π^2 terms. This fact and the intrinsic activity of this class of molecules (pI_{50} for the unsubstituted compound, that is when $\pi = 0$) again show that the region occupied by the substituted tetrazole moiety is very hydrophobic and not too specific. In fact, the phenyl group B in type III

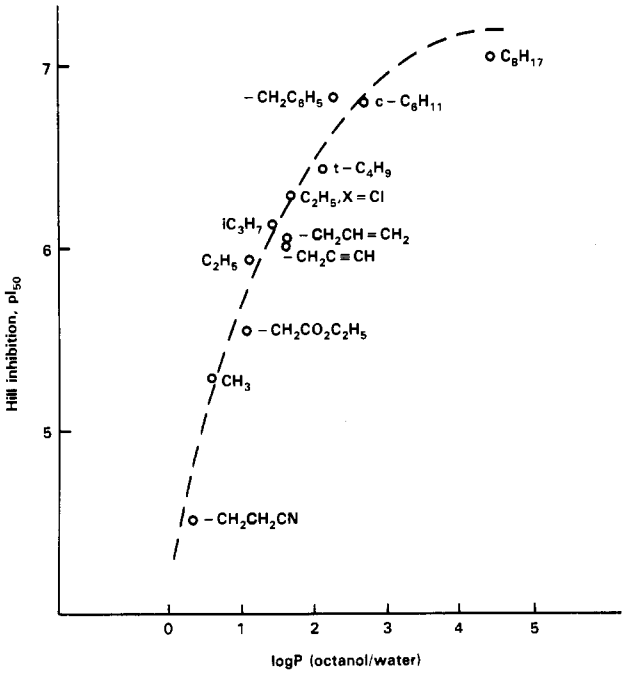


Figure 2. Hill inhibition activity as a function of lipophilicity, as measured by log P.

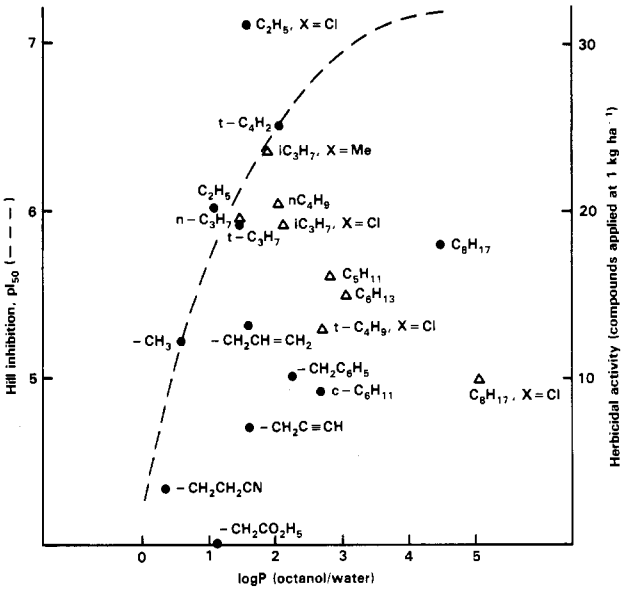


Figure 3. Preemergence herbicidal activity as a measure of lipophilicity (for symbols ● and △ see text).

molecules appears to be exhibiting a hydrophobic effect in the same way as type I molecules. To verify this, we measured the log P value for the unsubstituted phenyl derivative. This was found to be 2.07. Inserting this value in eq 1 gives a pI_{50} of 6.13, which is close to the measured value of 6.38 and to the value of 6.19 predicted by eq 7. This experimental correlation further supports the validity of eq 1.

Having analyzed the Hill inhibiting activity of the type I and type II tetrazole ureas, we assessed the primary screen herbicidal activity of these compounds. Type II tetrazole ureas are, in general, more phytotoxic than the corresponding type I molecules. Moreover, both classes of ureas are more active on broad-leaf plant species than on grasses. In order to acquire more information about the influence of the partitioning characteristics of these molecules on their herbicidal activity, we have analyzed the preemergence activity of type II compounds, applied at 1 kg ha^{-1} to four grass species, namely maize (*Zea mays*), rice (*Oryza sativa*), barnyard grass (*Echinochloa crus-galli*), and oat (*Avena sativa*). Broad-leaf species treated with this concentration of compound (and these four grass species treated at a higher concentration of 5 kg ha^{-1}) have given saturation levels of phytotoxicity for a number of the compounds considered. Thus, a quantitative assessment of phytotoxicity from primary screen data is only possible for compounds applied at the rate of 1 kg ha^{-1} on the grass species.

Herbicidal activity has been expressed as the sum of scores out of 9, based on visual inspection 10 days after application, for the four grass species. Total scores of 0 and 36 represent no activity and maximal phytotoxicity, respectively.

Figure 2 shows a plot of pI_{50} from the Hill inhibition against log P for the 12 type II compounds listed in Table II whereas Figure 3 relates this in vitro data to in vivo herbicidal activity expressed as a function of lipophilicity for the same compounds (● symbols) and for eight other compounds (△ symbols) that were not measured in vitro. In the case of the latter tetrazole ureas, log P values have been estimated from values determined for other type II molecules (see Table II).

Figure 3 shows that for at least seven of the tetrazole ureas in which R is a simple alkyl group with fewer than five carbon atoms (log $P < 2$), herbicidal activity parallels closely the Hill inhibition potency of these molecules as a function of log P. For compounds with alkyl groups bigger than butyl, a sharp fall occurs in herbicidal activity. The higher log P of these compounds may result in them having insufficient mobility in the plant to reach the site of action within the chloroplast. Other molecules that contain a more reactive R group (such as ester, alkene, and alkyne) show an appreciable discrepancy between in vitro and in vivo activity. Such compounds may not reach the site of action due either to chemical reaction or to metabolism to less toxic compounds.

The log P of around 2 that is observed for "optimum" herbicidal activity for the type II tetrazole ureas is lower than that reported for other simple phenylureas. For example, the values for the commercial phenylureas diuron and isoproturon are 2.68 (Briggs, 1981) and 2.87 (Kakkis et al., 1984), respectively. We had also previously shown (Camilleri et al., 1987) that, in the case of simple phenylureas substituted in the 3- and 4-positions of the phenyl rings, high herbicidal activity is observed even at log P values as high as 3.5. It is possible that simple phenylureas partition between the point of contact (foliage) to the site of action (chloroplast) via a pathway different from that taken by the tetrazole ureas. Such variation in transport properties can also cause differences in rates of metabolism.

The present investigation in the area of phenylureas has shown that the tetrazole derivatives show in vitro behavior that is broadly in agreement with the requirements of a PS II inhibitor, that is a lipophilic moiety that can interact with a hydrophobic zone and an amide function that can interact, possibly via a charge-transfer mechanism, with an amide receptor site located near the hydrophobic zone of the 32-kDa protein. As more information is generated concerning the nature and function of the urea binding site on this protein, the greater will be the chance of designing other PS II inhibitors that show herbicidal activity.

Registry No. **1**, 117121-32-1; **2**, 117121-33-2; **3**, 117121-34-3; **4**, 117121-35-4; **5**, 117121-36-5; **6**, 117121-37-6; **7**, 117121-38-7; **8**, 117121-39-8; **9**, 117121-40-1; **10**, 117121-41-2; **11**, 117121-42-3; **12**, 117121-43-4; **13**, 117121-44-5; **14**, 117121-45-6; **15**, 117121-46-7; **16**, 117121-47-8; **17**, 117121-48-9; **18**, 117121-49-0; **19**, 117144-73-7;

20, 117121-50-3; 21, 117121-51-4; 22, 117121-52-5; 23, 117121-53-6; 24, 117121-54-7; 25, 117121-55-8; 26, 117121-56-9; 27, 117121-57-0; 28, 117121-58-1; 29, 117121-59-2; 30, 117121-60-5; 31, 117121-61-6; 32, 117121-62-7; 33, 117121-63-8; 34, 117121-64-9.

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Effect of Soil and Foliar Daminozide Applications on Residue Levels in Peanut

Craig S. Kvien,* Richard A. DePalma, Art R. Raczynski, and Lesle M. Hellmann

Daminozide is used in the Southeast United States to control excess peanut (*Arachis hypogaea* L.) vine growth. Two states now require processed food to meet a none detected level of daminozide by 1990. This study determined the within-plant concentration and location of daminozide residues resulting from soil carryover of daminozide and from foliar applications of daminozide. Applications of 1.43 kg ha^{-1} daminozide to the soil immediately before planting resulted in no residue in any plant part at harvest. Plants treated with either a single foliar application of 0.95 kg ha^{-1} at 42 days after planting (DAP) or 0.95 kg ha^{-1} at 42 DAP plus 0.48 kg ha^{-1} at 86 DAP had mature fruit residues of 0.27 and 4.5 ppm, respectively. Foliar-applied daminozide is translocated throughout the plant. Residues in the foliage are predictive of residues in the seed. Foliar samples taken before harvest can be used as a diagnostic tool to locate daminozide-treated plants.

One of the major uses of plant growth retarding chemicals in the Southeast United States is to control excess peanut (*Arachis hypogaea* L.) vine growth (N'Diaye, 1980). Since the peanut is a perennial (Hoehne, 1940) with an indeterminate fruit set pattern and season-long shoot growth, harvesting and plant disease problems often result from excessive vine growth.

To prevent excess vine, some peanut growers have applied the plant growth retarding chemical daminozide to their crop (Brown and Ethredge, 1974; N'Diaye, 1980; Ohaly, 1985; Kvien et al., 1987). Although daminozide is both xylem and phloem mobile, plant growth regulating activity is dependent on foliar absorption since daminozide is rapidly degraded in the soil (Rothenberger, 1964; Moore, 1968; Uniroyal, 1981).

Department of Agronomy, University of Georgia Coastal Plain Experiment Station, P.O. Box 748, Tifton, Georgia 31793 (C.S.K.), The Procter and Gamble Company, Winton Hill Technical Center, 6071 Center Hill Road, Cincinnati, Ohio 45224 (R.A.D., A.R.R.), and Hill Top Biolabs, Inc., P.O. Box 429501, Cincinnati, Ohio 45242 (L.M.H.).

Two states now require processed food to have a none detected level of daminozide by 1990. New analytical techniques have lowered detection limits from 0.1 ppm for apple products or 2 ppm for peanut products to 0.01 ppm for all food products (Wright, 1987; Conditt and Baumgardner, 1988).

The studies that determined daminozide was not carried over from one cropping season to the next were conducted at the 2 ppm detection limit (Rothenberger, 1964). The potential for planting peanut on land treated with daminozide the previous season exists. Therefore, it is important to know whether these peanuts will meet the lower daminozide residue requirement. This study was conducted to determine the within-plant concentration and location of daminozide residues resulting from soil carryover of daminozide and from foliar applications of daminozide.

MATERIALS AND METHODS

This greenhouse experiment was conducted in 4-L pots arranged in a randomized complete block design with five treatments, three replications, and six pots per replication–treatment combination (90 total pots). The five experimental treatments were as follows: (1) A control soil

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