years in succession was negligible. Rahn and Baynard (12) found that monuron applied at 3.6 pounds per acre in two applications for 3 years in succession did not persist from one year to the next. When monuron was applied at 6.4 pounds per acre, phytotoxicity persisted from one year to the next, but accumulation did not occur.

In Arizona, the same plots were sprayed each year for 8 years with fenuron, monuron, or diuron at 0.8 and 1.6 pounds per acre for selective weed control in cotton (1). Although carry-over from one year to the next sometimes occurred, the herbicides did not appear to accumulate. Similar results were obtained from a 6-year field experiment in California (1).

In another experiment in California (3), plots of Yolo clay were sprayed with 0.25, 0.5, 1, and 2 pounds per acre of monuron and diuron in November for control of weeds in spinach. Applications were repeated each fall for 4 years, and persistence of the herbicides was determined in the greenhouse by quantitative bioassay of soil samples. Residues were detected approximately 6 months after each application of 2 pounds per acre of monuron and diuron and 1 pound per acre of monuron. Twelve months after application, measurable residues were detected only after the fourth annual application of 2 pounds per acre. This residue the fourth year was probably due to weather conditions as observed by Arle *et al.* (1); however, the possibility that a slow accumulation over the 4-year period occurred cannot be ruled out. If some accumulation occurred, the magnitude was not great.

Calculations based on the concept that the disappearance of the phenylurea herbicides conforms to a first-order rate equation show possible accumulation levels in soils. The theoretical curves in Figure 1 are based on the same principle as the curves of Hill *et al.* (7), and show the concentration of herbicide as a function of time in soil sprayed each year with 2 pounds per acre. An 80% loss per year was assumed as a reasonable minimum rate of loss of phenylurea herbicides for most soil type-environment situations in the U. S. Inactivation is greater than 80% in many cases (7). Figure 1 shows that if the same soil was sprayed annually with 2 pounds per acre of a herbicide, and if 80% of the herbicide dissipated each year, the amount in the soil immediately before reapplication would eventually approach 0.5 pound per acre. The amount in the soil immediately after application would approach 2.5 pounds per acre. Different rates of application or different loss assumptions would, of course, change the curves in Figure 1.

Rates of inactivation of herbicides vary tremendously in response to differences in soils and climate. Carry-over of monuron and diuron can be expected under some conditions; but results indicate that possibilities of massive accumulation in soils are nil.

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METABOLISM OF HERBICIDES

Metabolism of α-Chloro-*N,N*-diallylacetamide(CDAA) and 2-Chloroallyl-*N,N*-diethyldithiocarbamate(CDEC) by Plants

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THE METABOLISM of pesticides in general has received wide and intensive study, particularly within the past decade. These investigations have been initiated in many instances because of a desire and need to know the persistence, metabolism, and fate of subsequent degradation products of a given pesticide in crop plants. In many cases, such studies have resulted in collateral findings regarding detoxification mechanism, possible modes of action, bases of selectivity, bases of resistance, and other facts pertinent to the fields of pharmacology, physiology, and biochemistry. Thus, the development of modern pesticides has also had a direct and indirect influence upon the development of modern biology.

This symposium is directed toward reviewing our knowledge of the metabolic fates of various herbicides in plants, animals, and soil. This paper reviews work on two pre-emergent herbicides which possess remarkable qualities of specificity, particularly within the monocotyledenous species of plants (*1–4*).

The first material is α-chloro-*N,N*-diallylacetamide (CDAA) (Randox, registered Monsanto trademark). This grass-specific, pre-emergent herbicide is used quite widely, particularly in corn and soybeans, for the control of foxtail, brome grass, cheat grass, crabgrass, and certain broadleaf weeds (*2, 4*). It is an amber liquid, highly soluble in organic solvents, with a fair degree of water solubility (ca. 1%).

Two types of studies were undertaken with this material—one in which the carbonyl carbon was labeled with C^{14} and an other where the allyl moiety was labeled with C^{14}. Treating soil seeded to various crop plants with the

The metabolism of C^{14}-labeled CDAA indicated that it was rapidly converted into known naturally occurring products. The chloroacetic portion of the molecule was converted to glycolic acid. The allylic groupings of the molecule were readily disrupted as measured by the evolution of $C^{14}O_2$ from the middle carbon of the allylic radical. The metabolism of the 2-chlorallyl moiety of C^{14}-labeled CDEC indicated that the plant was capable of liberating the 2-carbon of the allyl moiety as $C^{14}O_2$. One of the primary metabolic breakdown products of the 2-chloroallyl grouping was lactic acid. The results indicate that neither of these grass-specific, pre-emergent herbicides should present residue problems in plants inasmuch as the crop plants normally treated with these chemicals are capable of metabolizing the molecules to naturally occurring metabolic products. The results further indicate that plants have the capacity for disrupting allylic moieties in an efficient and rapid manner.

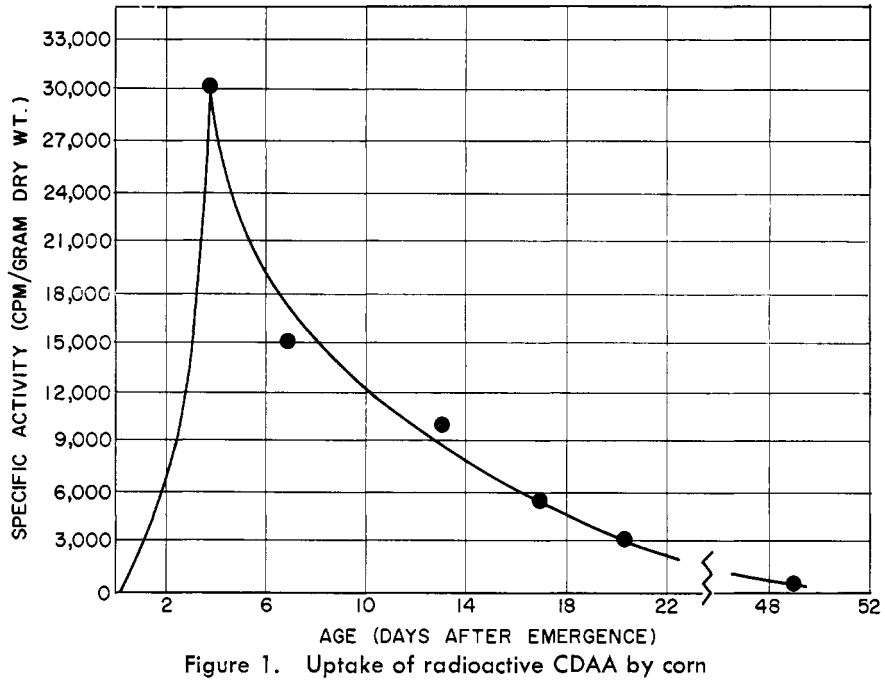

Figure 1. Uptake of radioactive CDAA by corn

labeled herbicide showed that the selectivity of this herbicide was not due to a lack of uptake from soil (Figure 1). While the curve shown is for corn, a similar uptake curve was obtained for soybeans as well. The uptake for soybeans was about three times the level of corn.

Metabolism of Chloroacetyl Moiety of CDAA

After the material was shown to be readily taken up by the plants, attempts were made to determine whether the material in the corn plants was in fact CDAA. Prior to doing this, the recovery procedure was established, and the results indicated that recoveries were greater than 90% at 0.1 p.p.m. concentrations of CDAA. A bioassay technique was developed to analyze various plant extractives for CDAA-like activity. Table I shows the standard results for CDAA response, as well as that from the corn plant extractives. The procedure used was as follows. Ten rye grass seeds were germinated in 50 ml. of aqueous solutions at 25° C. After 5 days of development, the seeds were removed and the hypocotyls measured. A growth response was readily demonstrable even at 0.01 p.p.m. of CDAA. In extracts from 4-day-old treated plants, less than 0.01 p.p.m. of CDAA could be detected by bioassay as against a concentration of 0.12 p.p.m. based on the amounts of radioactivity found. These data indicated that essentially complete metabolism of the molecule had taken place prior to the fourth day following emergence of the corn seedlings.

Chromatographic analyses were made on the extracts to determine the number and types of major radioactive components present in the extracts. Table II shows the R_f values of major compounds which could be present as a result of breakdown of the CDAA molecule. The results shown in Table III represent chromatographic analyses of corn plants which had been treated

Table I. Bioassay of Corn Extracts[a] (Carbonyl-C^{14}-CDAA Treatment)

Concentration of CDAA (P.P.M.)	Concentration of CDAA Based on Radioactivity (P.P.M.)	Growth[b] (P.P.M.)	Concentration of CDAA Based on Bioassay (P.P.M.)
	CONTROL		
..	..	21.3	..
	CDAA		
0.1	..	3.0	0.1
0.05	..	4.8	0.05
0.01	..	8.6	0.01
	PLANT EXTRACT (4 DAYS AFTER EMERGENCE)		
..	0.12	16.6	0.01
..	0.06	20.8	0
	PLANT EXTRACT (7 DAYS AFTER EMERGENCE)		
..	0.06	21.5	0
..	0.03	19.9	0

[a] The standards all contained plant extractives from untreated plants equivalent in total to those of treated plant extracts.
[b] The data presented are the means of 2 replicates with 10 seeds per replicate.

Table II. R_f Value of Several Compounds

Compound	Solvent System[a] a	b	c
CDAA	0.89	0.91	0.93
Alpha hydroxy analog of CDAA	0.89	0.76	0.89
Glycolic acid	0.00	0.61	0.59
Glyoxylic acid	0.00	0.47	0.15
Lactic acid	0.02	0.67	0.71
Glyceric acid	0.00	0.75	0.80
Oxalic acid	0.00	0.00	0.49
Chloroacetic acid	0.48	0.83	0.86

[a] Solvent *a:* benzene–methanol–H_2O (10:5:5)
Solvent *b:* 80% aqueous phenol
Solvent *c:* butanol–acetic acid–H_2O (4:1:5)

Table III. Chromatographic Analyses of Corn Extracts

Plant Extract (Days after Emergence)	Solvent a		Solvent b		Solvent c	
	R_f	% Radioactivity	R_f	% Radioactivity	R_f	% Radioactivity
4	0.00	92	0.64	98	0.63	97
	0.64	5	0.89	2	0.94	3
7	0.00	88	0.64	68	0.55	14
	0.21	4	0.88	20	0.69	68
	0.65	4			0.86	15
	0.90	5				
13			0.13	11	0.19	11
			0.72	63	0.55	7
			0.89	16	0.75	62
					0.88	6
17			0.30	5	0.00	6
			0.49	5	0.10	4
			0.70	70	0.65	69
			0.80	11	0.81	16

Table IV. CO_2 Train Results with Carbonyl-C^{14}-CDAA-Treated Corn (24 Days)

Fraction	Total Activity (C.P.M.) $\times 10^7$	% Radioactivity Based on: Total	Plant
CO_2 collected	0.395	16.5[a]	54.4[a]
Plant	0.331	13.8	45.6
Soil	1.675	69.7	

[a] Data not corrected for $C^{14}O_2$ liberated by soil microflora.

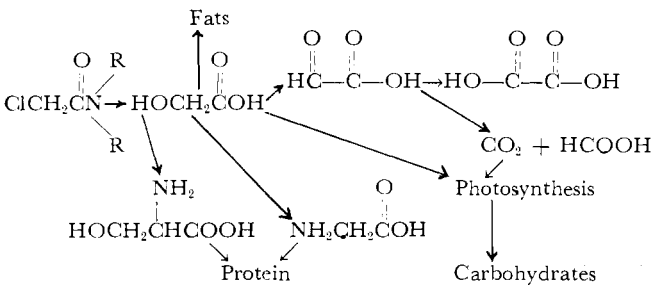

Figure 2. Possible routes of glycolic acid

Table V. CO_2 Train Results with Allyl-C^{14}-CDAA-Treated Corn (13 Days)

Fraction	Total Activity (C.P.M.) $\times 10^7$	% Radioactivity Based on: Total	Plant
CO_2 collected	0.56	7.8 (6.3[a])	17 (13.6[a])
Plant	2.74	38.2	83
Soil	3.87	54.0	

[a] Data corrected for microbial breakdown of CDAA equivalent to 0.11×10^7 c.p.m.

with carbonyl-labeled CDAA and harvested after the periods indicated. Four days following emergence of the corn, the primary radioactive material was at R_f 0.00 in solvent *a* and R_f 0.64 in solvent *b*. These R_f values coincided with those for glycolic acid. A similar pattern was noted 7 days following emergence of the corn plants; however, more radioactive compounds were detected in this later extract. After 13 and 17 days, additional compounds were detected in the system, as might be expected. The results show that CDAA was not present, or if present, was there in only a trace amount. No hydroxy analog of CDAA was detected nor was the chloroacetic acid moiety detected. Therefore, glycolic acid and possibly lactic acid or glyceric acid may be present. A number of other solvent systems were investigated, and cochromatographic analyses with unlabeled glycolic acid in seven solvent systems with alcoholic bromocresol purple (0.01% solution) as a color-detection agent established that glycolic acid was, in fact, the major radioactive product formed from the breakdown of C^{14}-CDAA.

Additional information was obtained by growing carbonyl-C^{14}-CDAA-treated corn plants in a closed system in which CO_2-free air was introduced to the system and CO_2 evolution by the plant was assayed for radioactivity. Table IV shows that more than 50% of the radioactivity absorbed through the root system was evolved as $C^{14}O_2$, indicating that the plant readily degraded the CDAA molecule. This was also consistent with the finding of glycolic acid in the system.

Figure 2 shows the possible routes of glycolic acid once it is formed. If the chloroacetamide yields the glycolic acid moiety by hydrolysis at the amide and alpha-chloro linkages, then one would expect to find radioactivity in all fractions of the plants as well as in the CO_2 liberated by the plants.

Metabolism of Allylic Moieties of CDAA in Resistant Plants

The allylic radicals were tagged in the 2-carbon position and the plants treated as described for carbonyl work. The CO_2 train system was again utilized to measure $C^{14}O_2$, and Table V shows the data from studies with allyl-C^{14}-CDAA-treated corn. In such a system, there is undoubtedly some photosynthetic reincorporation of respiratory carbon dioxide into the plants because of the removal of CO_2 from the air entering the system. Also, some microbial breakdown of CDAA occurs. Chromatographic analyses of extracts of these plants did not elucidate the route of breakdown, possibly because of the lability or volatility of some of the intermediate products. No diallylamine could be found in extracts nor could any monoallylamine be detected, two products which might be expected as the result of the metabolism of this moiety. Other possible degradation products sought for but not found included acrolein, allyl alcohol, and acrylic acid.

To establish further that the breakdown of the CDAA molecule was complete and that accumulation of some specific product was not taking place, plants were treated with the tagged material and grown to maturity. Following maturation, the crops were harvested and fractionated for assay of radioactivity. Table VI shows the distribution of radioactivity. There is, in general, low level distribution of radioactivity among all fractions isolated. Since each fraction is morphologically, as well as in many instances chemically, different from the other, there is a random distribution of radioactivity throughout the plant constituents, suggesting again that no unusual metabolite is formed as a result of the degradation of CDAA, but that the carbon atoms are randomized and incorporated through normal metabolic pathways into many natural products. A similar picture was developed for soybeans and many other crops, and the metabolism in each instance yielded glycolic acid when carbonyl-labeled CDAA was used. When allyl-labeled CDAA was used,

Table VI. Radioactivity of Corn Seed Fractions

Fraction	Specific Radioactivity, C.P.M. per Gram	Concentration of Radioactivity Expressed as P.P.M. C^{14}
Hulls		
Whole hulls	33.0	3.7
Petroleum ether extract	8.3	0.9
Aqueous extract	16.1	1.8
Residue	30.5	3.4
Germs		
Whole germs	26.9	3.0
Petroleum ether extract	6.4	0.7
Santomerse soluble	4.6	0.5
Protein	10.1	1.1
Residue	4.7	0.5
Endosperm		
Whole endosperm	22.6	2.5
Petroleum ether extract	5.0	0.6
Aqueous extract	5.7	0.8
Protein	4.4	0.5
Starch	16.9	1.9

Table VII. Distribution of C^{14} after Fractionation of Cabbage

Crop	% Radioactivity in Fractions[a] Acetone-insoluble residue	Ether	Cation	Anion	Neutral
Cabbage	17.4	4.65	16.8	36.8	9.6

[a] The percentages represent actual recovered radioactivity and do not total 100% since some loss was incurred on the columns.

Table VIII. Distribution of Radioactivity in Cation Fraction from CDEC-Treated Cabbage

Amino Acid	Color	Radioactivity (D.P.M.)
Aspartic acid	Purple	27
Lysine	Purple	625
Asparagine	Orange brown	1875
Cysteic acid	Purple	0
Serine	Purple	232
Glycine	Red purple	172
Glutamic acid	Purple	294
Histidine + glutamine	Purple	2000
Methionine sulfoxide	Purple	650
Threonine	Purple	334
Alanine	Purple	915
α-Amino butyric acid	Purple	34
Tyrosine + γ-Amino butyric acid	Purple	115
Tryptophan	Purple	
Valine + phenylalanine	Purple	333
Leucine	Purple	273
Proline	Yellow	124
Isoleucine	Purple	234
Arginine	Purple	180
Blank 1	...	115
Blank 2	...	0
Blank 3	...	0
Blank 4	...	45
Unknown 1	Purple	0
Unknown 2	Purple	68
Unknown 3	Purple	47
Unknown 4	Purple	119
Unknown 5	Purple	145

Table IX. R_f Values of Major Radioactive Peaks

Source	Fraction	Solvent[a] 1	2	3	5	6
Cabbage	Ether	0.59, 0.68 0.80				0.0, 0.66 0.93
	Neutral	0.54, 0.84	0.78, 0.92	0.39, 0.51 0.67, 0.79		
	Anion		0.33, 0.57 0.70	0.11, 0.44 0.57, 0.69	0.14, 0.32 0.56, 0.84	
CDEC	...	1.0	1.0	1.0	1.0	1.0
Lactic acid	...	...	0.72	0.68	0.87	
Shikimic acid	...	...	0.56	0.49	0.61	
Malic acid	...	...	0.43	0.49	0.62	

[a] Solvent 1: methanol–acetone (1:1); solvent 2: 70% aq. phenol; solvent 3: butanol–acetic acid–H_2O (4:1:5); solvent 5: ether–88% formic acid–water (5:2:1); solvent 6: petroleum ether–ethyl ether (3:1).

Table X. Cochromatography of Anion Fractions

Solvent System	Tube 22[a] + Glycolic Acid: Radioactive spot (R_f)	Tube 22 + Glycolic Acid: Color spot (R_f)	Tube 22 + Lactic Acid: Radioactive spot (R_f)	Tube 22 + Lactic Acid: Color spot (R_f)
2	0.70	0.68	0.71	0.71
3	0.68	0.60	0.73	0.73
5	0.89	0.77	0.89	0.89

[a] Tube 22 was selected for cochromatography because it contained the radioactive acid which represented about 85% of the radioactivity in the anion fraction. The color spot was developed with a bromocresol purple spray.

substantial quantities of $C^{14}O_2$ were ejected by the plants, and a random distribution of C^{14} in the various chemical and morphological units of the mature plants was found.

Metabolism of 2-Chloroallyl Moiety of CDEC in Resistant Plants

The next pre-emergent herbicide studied was 2-chloroallyl-*N*,*N*-diethyldithiocarbamate (CDEC) (Vegedex, registered Monsanto trademark). This compound is also a liquid, highly soluble in organic solvents but very insoluble in water as contrasted with CDAA. It is useful in controlling the same type of grass species and broad leaves as CDAA and finds its principle use in vegetable crops, particularly on lighter soils where leaching can be a problem (*7*). In the case of CDEC, particular interest was directed toward studying the metabolic fate of the 2-chloroallyl moiety, and it was therefore labeled in the 2-position with C^{14}. Four-week-old cabbage sets were treated at 6 pounds per acre with the C^{14}-CDEC; 21 days later the cabbage sets were harvested, homogenized, and extracted with 80% aqueous acetone, a solvent system which completely solubilizes CDEC. The distribution of radioactivity between the acetone-insoluble and -soluble fractions was 16.7 and 83.3%, respectively. The acetone extract was stripped of its acetone, and the aqueous solution resulting (pH 6.5) was extracted with ether.

The aqueous solution was then put through an IR 120 (H^+) cation exchange column followed by a Dowex 1-10X anion exchange column, the latter being subjected subsequently to gradient elution analysis with formic acid. The distribution of radioactivity of these various fractions is shown in Table VII. There is a general distribution of radioactivity among all fractions isolated, suggesting substantial breakdown of the 2-chloroallyl moiety as well as of the parent molecule. These various fractions were subjected to paper chromatographic analyses to identify the materials. A number of radioactive components were found in each extract chromatographed, totaling a minimum of 11 radioactive components, each dif-

ferent from one another. The distribution of the minimum number of radioactive components in the ether, anionic, and neutral fractions was 3, 4, and 4, respectively. The distribution of radioactivity in the cation fraction (developed by two-dimensional chromatography) (Table VIII) indicated that almost all amino acids were labeled with C^{14}, with highest labeling in asparagine and the combination histidine plus glutamine. These amino acids might be expected to have lower turnover numbers, hence higher labeling could result because of less dilution during growth.

Table IX summarizes R_f values of major radioactive peaks found in several of the extracts, as well as some standard values for compounds suspected to be present in the extracts.

Because the anion fraction contained so much of the total radioactivity (36%), it was further analyzed by using gradient elution procedures. Three radioactive organic acids were found in this fraction, with 85% of the radioactivity associated in one fraction (tube 22). This cut was cochromatographed with lactic acid and glycolic acid, and the results are shown in Table X.

Since lactic acid appeared to be present as one of the major metabolic components, it was of interest to determine whether this material was formed by direct breakdown of the 2-chlorallyl grouping or whether it was formed indirectly, perhaps by the liberation of $C^{14}O_2$ and reincorporation of CO_2 into lactate. With the isotope dilution technique, 0.5 ml. of 85% aqueous lactic acid was added to tube 22, which did not contain sufficient acidity to estimate the amount of labeled lactate that might be present. The lactic acid was distilled using a molecular still, and the *p*-bromophenacyl derivative was then made. The derivative was recrystallized several times to constant specific activity. The melting point of the ester was identical with that reported in the literature (112°–113° C.). By making the correction for the estimated isotope dilution (8500), a specific radioactivity of the original lactic acid was calculated to be 3.5×10^5 disintegrations per minute (d.p.m.) per mg. This figure was within a factor of 8 of the original specific activity of the labeled material used, suggesting that lactic acid may be formed directly from the 2-chloroallyl moiety. This is particularly significant in that the specific activities of all the other fractions mentioned previously were of the order of 10^3 d.p.m. per mg. compared to the anion fraction which had a specific activity 100 times greater.

Discussion

The data presented illustrate the ability of resistant crop plants to metabolize the CDAA- and CDEC-type herbicide rapidly and extensively to naturally occurring products. The results further indicate that plants have a ready ability to metabolize allylic-containing material even when chlorinated, although at present the exact mechanism by which this metabolic degradation occurs is not known. Probably this rapid metabolic degradation leads to the high degree of resistance shown by the crop species toward these chemicals. Thus not only are desirable plants able to detoxify the chemicals completely, but degradation is carried out to the extent that residues of the parent compound or its component parts are nonexistent.

The general trend for selectivity of pesticidal activities may reside in the ability of plants to metabolize and detoxify the compounds at different rates rather than by inhibition of enzyme systems unique to certain species of plants. This aspect of selectivity, while studied to some extent, requires additional intensive study as to the kinetics of detoxifying biochemical reactions particularly as a springboard toward the better design of selective pesticides.

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METABOLISM OF HERBICIDES

The Metabolism of *S*-Propyl-1-C^{14} *n*-Butylethylthiocarbamate (Tillam-C^{14}) in Rats

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SEVERAL thiolcarbamates have been introduced recently as pre- and postemergence herbicides on forage legumes and certain vegetable and field crops. Their mechanism of action is not fully understood. Since some carbamates are active as weed killers and cause nuclear changes in cells, thiolcarbamates might be toxic to cells also. The widespread use of these compounds in weed control undoubtedly raises a residue problem in foods. The solution to this problem requires information on the quantities of the herbicide present in the crops, and on whether or not a given rate of intake of herbicides is injurious to human health. To learn how quickly an animal can detoxify and eliminate the ingested herbicide from the body will also provide information relating to health hazard. Tillam-C^{14} is easily degraded by plant cells (*2*), and the radioactivity is incorporated in the respiratory CO_2. The purpose of this investigation was to characterize the excretory pattern of orally administered Tillam-C^{14} in the rat, and to study tissue residues following administration.

Experimental

Tillam-C^{14}, 3.11 mc. per mmole, was first dissolved in ethanol to give 6.57 mg. of Tillam per ml. of stock solution. No chemical or C^{14} impurities of this Tillam-C^{14} sample were detected by gas liquid chromatography. Twenty per cent alcohol solutions containing various amounts of Tillam-C^{14} were prepared immediately prior to administration. Adult rats of the Wistar strain (4 to 6 months of age) were fed orally a given amount of Tillam-C^{14} by means of a