Metabolism of Clomazone Herbicide in Soybean

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The metabolism of 2-[(2-chlorophenyl)methyl]-4,4-dimethyl-3-isoxazolidinone (clomazone) was studied in soybean plants grown in the greenhouse using ^{14}C-radiolabeled clomazone at 1.1 and 2.2 kg of ai/ha. Isolation and identification of clomazone metabolites from soybean plants at 30 and 60 days after treatment indicated that the major metabolic processes included dealkylation of the parent chemical at the alkylamide linkage and conjugation of the resulting chlorobenzyl moiety to form its corresponding glycoside(s). Other minor metabolic routes included monohydroxylation of clomazone on either the aromatic or the isoxazolidinone moieties with subsequent formation of their corresponding glycosides. Additional polar metabolites that may result either from extensive degradation or from amino acid conjugations of parent compound or its intermediate metabolites were also observed.

INTRODUCTION

Clomazone is a herbicide developed by FMC Corp. for use against many species of annual broad-leafed and grassy weeds (Warfield et al., 1985; Chang et al., 1987). It is currently being used for weed control in soybean under the trademark Command herbicide. Early clomazone studies on cowpea (*Vigna unguiculata* L., cv. California Blackeye) indicated that the compound has a direct effect on chloroplast development rather than on photosynthesis (Duke and Kenyon, 1986; Duke and Paul, 1986). Further studies suggested that clomazone blocks both diterpene and triterpene synthesis (Duke et al., 1985). In 1987 Sandmann and Boger demonstrated that clomazone inhibits the terpenoid pathway before or at the prenyl pyrophosphate step. To explain the susceptibility difference of certain crops to clomazone, Weston and Barret in 1989 studied tolerant bell pepper (*Capsicum annum* L.) and susceptible tomato (*Lycopersicon esculentum* Mill.) and reported that differences in selectivity could not be based solely on differential absorption, translocation, or metabolism. Moreover, Norman et al. (1990) reported that soybean (*Glycine max* L.) was more tolerant to clomazone relative to cotton (*Gossypium hirsutum* L., cv. Stoneville 825) when evaluated in both whole plant and cell suspension culture. Differential uptake was ruled out as a primary factor in clomazone selectivity.

Recently, Weimer et al. (1991) indicated that differences of susceptibility to clomazone between a tolerant (soybean) and a nontolerant (velvetleaf, *Abutilon theophrasti* Medik.) species could not be explained on the basis of differential metabolism. On the other hand, Vencill et al. (1990) suggested that differential root absorption of clomazone appeared to play a role in the differential response of the tolerant soybean and *Amaranthus hybridus* and susceptible *Amaranthus retroflexus* and *Amaranthus lividus*. Except for noting the presence of 2-chlorobenzyl alcohol as a metabolic breakdown product of clomazone, none of the previous papers discussed either the characterization of other individual clomazone metabolites or any detailed metabolic pathways in plants. In this paper, spectral and chromatographic characterizations of clomazone metabolites as well as its metabolic fate in soybean are discussed.

MATERIALS AND METHODS

Chemicals. Clomazone and related metabolite standards were synthesized at FMC Corp. Research and Development Center, Princeton, NJ (Chang et al., 1987). The radiolabeled compound, 2-[(2-chlorophenyl)(^{14}C)methyl]-4,4-dimethyl-3-isoxazolidinone (methylene label), was also prepared at FMC Laboratories using [^{14}C]-2-chlorobenzyl chloride purchased from Pathfinder Laboratories Inc. (St. Louis, MO). It had a specific activity of 26.8 mCi/mmol and was isotopically diluted with unlabeled clomazone to 0.6–8.7 mCi/mmol. Radiochemical purity was determined to be >99% by HPLC.

Plant Material. Soybean seeds (*G. max* [L.] Merr. cv. Corsoy) were inoculated with *Rhizobium japonicum*, and seeds were planted in 13 cm diameter pots at a depth of 1.2–2.5 cm in soil. The radioactive clomazone was mixed with an emulsifiable concentrate formulation blank and water, and the solution was applied to the pots using a DeVilbiss sprayer, at rates equivalent to 1.1 and 2.2 kg of ai/ha. Plants were grown under standard greenhouse conditions. One to two plants were harvested after 30 and 60 days. At each harvest interval, plant samples were weighed and ground in a Tekmar analytical mill (Tekmar, Cincinnati, OH) with liquid nitrogen, and individual samples were stored in the freezer (ca. −20 °C) for subsequent analyses.

Radioactivity Measurements. Levels of radioactivity in plant material before and after extraction were determined by combustion of 0.2–0.5-g subsamples in an Intertechnique JA101 sample oxidizer (IN/US Service Corp., Fairfield, NJ), and evolved $^{14}CO_2$ was trapped in Oxifluor cocktail (New England Nuclear, Boston, MA).

Radioactivity in the various plant extracts, HPLC fractions, and TLC scrapings was determined in 10–15 mL of either Insta-Gel (Packard) or RTU II (Eastman Kodak Co., Rochester, NY) scintillation cocktail. Samples were counted in a Beckman LS 7500 (Beckman Instruments, Fullerton, CA) or Packard 3385 Tri-Carb LSC (Packard Instrument Co., Downers Grove, IL) for 10 min or until a statistical accuracy of ±2% was obtained.

Extraction of Plant Metabolites. Pulverized plant tissue samples of ca. 50 g from 30- and 60-day harvest intervals were blended at room temperature with 3 times their weight of methanol, using a Tekmar Tissumizer, and then filtered. The combined methanolic extract was concentrated on a rotary evaporator until the methanol was removed. The remaining aqueous solution was partitioned with methylene chloride to give an organosoluble fraction containing the parent chemical and

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the nonconjugated metabolites, with the more polar (i.e., conjugated) metabolites remaining in the aqueous phase. The water-soluble metabolites were subjected to enzymatic hydrolysis using cellulase (Sigma Chemical Co., St. Louis, MO) in a pH 5 acetate buffer. The resulting aglycons were removed from the water using C18 solid-phase extraction (Sep-Pak, Waters Associates, Milford, MA) and subsequently eluted from the Sep-Pak with methylene chloride. The eluates were subjected to TLC and HPLC analysis and used in the preparative isolation and identification of individual metabolites by spectroscopic methods.

Chromatography and Spectroscopy. The organosoluble, nonconjugated metabolites, and aglycons released enzymatically were analyzed on 250 μm Analtech (Analtech, Inc., Newark, DE) silica gel plates using chloroform–methanol (98:2 v/v). Radioactive spots on TLC plates were located by autoradiography; radioactive areas on preparative plates were removed, eluted with chloroform–methanol (1:1 v/v), and quantitated. Eluted metabolites from TLC were further purified using reversed-phase HPLC. HPLC was by Waters Associates Model 710B wisp auto injector, Model 720 system controller, Model 730 data module, Model 6000A and M45 solvent delivery system, and Model 441 UV detector set at 214 nm, and a μBondapak C18 column (3.9 mm × 30 cm, 10 μm particle size). A gradient of acetonitrile–water was applied using Waters HPLC curve 4 at a flow rate of 2 mL/min. Solvent composition was 0–40% CH_3CN over 25 min, 40–100% CH_3CN for 1 min, and continued at 100% CH_3CN for an additional 7 min. Two RP-18 5 μm OD-GU 3 cm × 4.6 mm ID guard column cartridges were used. Purification of individual metabolites for GC/MS and NMR and resolution of metabolites F and G were accomplished with a RP Whatman Magnum 9 column ODS-2 (9.4 mm × 25 cm, 10.0 μm particle size, 9.57 mL void volume). A gradient of acetonitrile–water was applied using Waters HPLC curve 4 at a flow rate of 5 mL/min. Solvent composition was 0–40% CH_3CN over 25 min, continued at 40% for an additional 8 min. GC was performed on a Shimadzu GC-6AM system equipped with a Panax-Radio gas detector (Panax Nucleonics, Surrey RH1 2PP, England) and a flame ionization detector. A glass column 6 ft × 1/8 in. of 3% OV-17 on Chromosorb was used with 5% CO_2/argon gas as carrier, at a flow rate of 60 mL/min. Temperature was programmed at 70–285 °C at a rate of 8 °C/min with an injection port temperature maintained at 270 °C. MS (direct insertion) and GC/MS, EI and CI (isobutane, 0.7 Torr), were performed on a Varian MAT 311A or MAT 212 spectrometer, equipped with a Varian SS-200 data system. A 183 cm × 2 mm i.d. glass column packed with 3% OV-17 on Chromosorb was used, with helium as a carrier gas, at a flow rate of 25 mL/min. The temperature program was 150–260 °C at a rate of 10 °C/min, and the injection port was 250 °C.

NMR Spectroscopy. Solvent from purified metabolites was evaporated under a stream of dry nitrogen; metabolites were dissolved in "100%" acetone-d_6 in a 5-mm NMR tube. Spectra were recorded with a Varian NMR spectrometer. Chemical shifts were recorded as ppm (δ) downfield from TMS. In cases where metabolite quantities were very low, no TMS was added and chemical shifts were based on those of specific solvent signals.

Derivatization Procedure. Preparation of trimethylsilyl derivatives was conducted in Reacti-Vials using 5–20 μg of individual metabolites in 10 μL of pyridine and 100 μL of *N,O*-bis(trimethylsilyl)trifluoroacetamide reagent (Pierce, Rockford, IL). The mixture was heated at 60 °C for 2 h and the volume then reduced to ca. 10 μL prior to GC/MS analysis.

All metabolites were identified by comparison with authentic standards except for metabolite G, which was identified on the basis of extensive GC/MS and NMR analytical data.

RESULTS

Isolation and Identification of Individual Metabolites. Since nonconjugated metabolites accounted for 7.9% and 2.9% of the TRR in 30- and 60-day harvest intervals, respectively, (Table I) and were considered a relatively minor component of the TRR, identification of individual metabolites was instead done, for the most part, on the enzymatically released aglycons from the conjugated metabolite fraction, where TLC and HPLC analysis of metabolites revealed the presence of seven products designated A–G (Figure 2). Chromatographic characteristics (TLC) are shown in Table II. Identifications of metabolites B and D were not made due to insufficient quantities of material necessary for spectral analysis. Metabolites F and G cochromatographed on TLC but were resolved on HPLC. HPLC retention times for these clomazone metabolites are listed in Table III.

Table I. Distribution of ^{14}C Residues at Different Harvesting Intervals

fraction	% 30 days	% 60 days
nonconjugated metabolites[a]	7.9	2.9
conjugated metabolites	77.7	81.4
5-ketoclomazone (A)	(4.1)[b]	(3.7)
unknown (B)	(6.3)	(2.7)
2-chlorobenzyl alcohol (C)	(36.9)	(44.0)
unknown (D)	(6.8)	(2.5)
5-hydroxyclomazone (E)	(2.1)	(1.4)
5′-hydroxyclomazone (F) and (hydroxymethyl)clomazone (G)[c]	(15.1)	(16.0)
polar degradates	(6.4)	(11.1)
bound residue	14.4	15.7
total	100.0	100.0

[a] Nonconjugated metabolites included the parent chemical plus several minor metabolites. [b] Parenthetical values represent the actual percentages of each metabolite in the fraction. [c] Metabolites F and G were present in ca. equal amounts, based on HPLC analysis of the mixture.

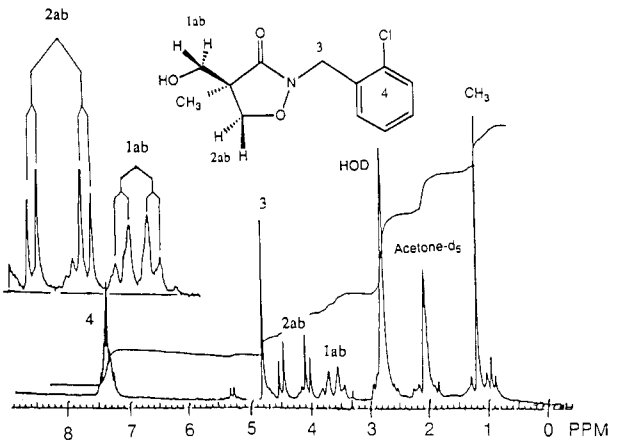

Figure 1. ^1H NMR spectrum of metabolite G (100 MHz, acetone-d_6).

Metabolite A, 2-[(2-Chlorophenyl)methyl]-4,4-dimethyl-3,5-isoxazolidinedione (5-Ketoclomazone). Metabolite A was isolated from the aglycon fraction using preparative TLC. It was the most volatile of all of the clomazone metabolites. Chromatographically, it was found to be less polar than clomazone by silica gel TLC with an R_f value of 0.73 (Table II) and by a reversed-phase (C_{18}) HPLC with a R_t of 28.92 min (Table III). Its structure was assigned by direct comparison of TLC R_f and HPLC R_t values with those of a synthetic standard of 5-ketoclomazone. The extreme volatility of metabolite A and the lack of enough sample precluded any spectroscopic analysis in this study. Metabolite A was, however, isolated prevously in sufficient quantities from a rat metabolism study of clomazone and was chemically and spectroscopically characterized (Wu et al., 1983).

Metabolite C, 2-Chlorobenzyl Alcohol. Metabolite C was isolated using preparative TLC and purified by C18 reversed-phase HPLC. It exhibited an R_f value of 0.38 on silica gel TLC plates (Table II) and a R_t of 14.67 min on HPLC (Table III). Metabolite C was found in both the aglycon fraction and the nonconjugated fraction. Identification was accomplished by TLC, HPLC, GC, cochro-

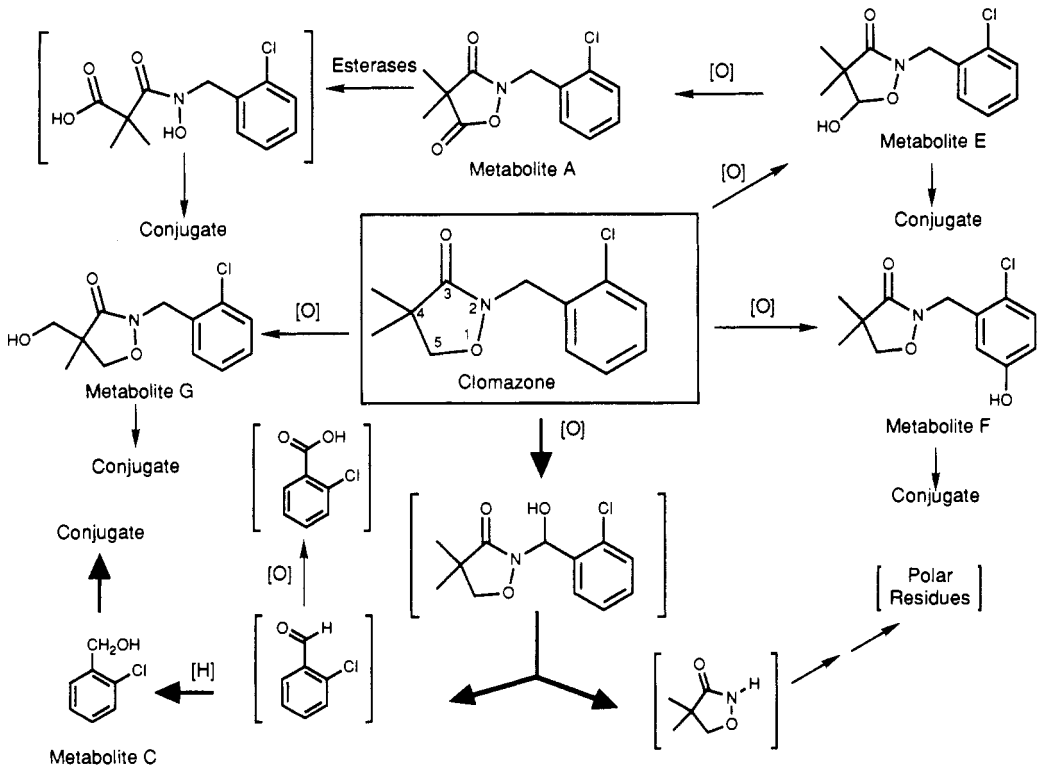

Figure 2. Proposed metabolic pathways of clomazone in soybean plants.

Table II. TLC[a] R_f Values for Clomazone and Its Metabolites

metabolite	R_f	metabolite	R_f
clomazone	0.62	unknown (D)	0.36
5-ketoclomazone (A)	0.73	5-hydroxyclomazone (E)	0.24
unknown (B)	0.45	5′-hydroxyclomazone (F)	0.18
2-chlorobenzyl alcohol (C)	0.38	(hydroxymethyl)clomazone (G)	0.18

[a] Solvent system $CHCl_3$–MeOH (98:2) using silica gel G 250 μm.

Table III. HPLC Retention Times[a] for Clomazone and Its Metabolites

metabolite	R_t, min	metabolite	R_t, min
clomazone	26.17	5-hydroxyclomazone (E)	17.12
5-ketoclomazone (A)	28.92	5′-hydroxyclomazone (F)	18.72
2-chlorobenzyl alcohol (C)	14.67	(hydroxymethyl)clomazone (G)	16.72

[a] HPLC R_t are those generated using a μBondapak column. Conditions used are mentioned under Materials and Methods. Metabolites B and D were not analyzed by HPLC.

matography with an authentic reference standard of 2-chlorobenzyl alcohol, and MS. Comparative GC/MS-EI of metabolite C also agreed with that of the standard, 2-chlorobenzyl alcohol. The mass spectrum displayed a molecular ion (M^+) at m/z 142, 144 (3:1 ratio). In addition, prominent ions at m/z 107 of $(M - Cl)^+$, m/z at 125 of $(M - OH)^+$, and a base peak at m/z 77, 79 were observed.

Metabolite E, 2-[(2-Chlorophenyl)methyl]-5-hydroxy-4,4-dimethyl-3-isoxazolidinone (5-Hydroxyclomazone). This metabolite was isolated by preparative TLC (R_f = 0.24) and then purified by HPLC (R_t = 17.12 min). Metabolite E was found in both the aglycon fraction and the nonconjugated fractions. The GC/MS-EI and GC/MS-CI spectral data of metabolite E, as well as spectral characteristics of its trimethylsilyl derivative, agree with those of a synthetic reference standard. The EI mass spectrum displayed a molecular ion (M^+) at m/z 255 and fragmentation ions of $(M - Cl)^+$ at m/z 220, $(C_7H_6Cl)^+$ at m/z 125, 127, and other ions at m/z 102, 99, and 77.

Metabolite F, 2-[(2-Chloro-5-hydroxyphenyl)methyl]-4,4-dimethyl-3-isoxazolidinone (5′-Hydroxyclomazone). Metabolite F was isolated along with metabolite G as one band from preparative TLC (R_f = 0.18) but separated and purified from metabolite G using HPLC (R_t = 18.72 min). This metabolite was detected mainly in the aglycon fraction. Metabolite F was identified by ^1H NMR, GC/MS, and chromatographic comparison with a synthetic standard. It gave the following spectral data: ^1H NMR δ 1.25 (s, $2CH_3$), 4.12 (s, CH_2ON), 4.74 (s, $CH_2C_6H_4OCl$), 6.83 (B of ABX, 4′-H, J_{AB} = 3 Hz), 6.96 (d, A of ABX, 6′-H, J_{AB} = 3 Hz), and 7.27 (X of ABX, 3′-H, J_{BX} = 9 Hz); CI mass spectrum, quasimolecular ion $(M + H)^+$ at m/z 256 and additional ion fragments were observed of $(M - HCl)^+$ at m/z 220 and of $(C_7H_6ClO)^+$ at m/z 141. The CI mass spectrum of the trimethylsilyl derivative displayed a quasimolecular ion of $(M + H)^+$ at m/z 328, 330 (3:1 ratio).

Metabolite G, 2-[(2-Chlorophenyl)methyl]-4-(hydroxymethyl)-4-methyl-3-isoxazolidinone [(Hydroxymethyl)clomazone]. Metabolite G was preparatively isolated from metabolite F using HPLC (R_t = 16.72 min). Metabolite G also was detected mainly in the aglycon fraction and was identified by ^1H NMR and GC/MS: ^1H NMR (Figure 1) δ 1.22 (s, CH_3), 3.51–3.77 (AB quartet, J_{AB} = 11 Hz, CH_2OH), 4.06–4.50 (AB quartet, J_{AB} = 8.5 Hz, CH_2ON), 4.81 (s, $CH_2C_6H_4Cl$), and 7.41 (complex m, $CH_2C_6H_4Cl$, 4 aromatic protons); EI mass spectrum, molecular ion (M^+) at m/z 255, additional ion fragments were observed of $(M - Cl)^+$ at m/z 220, base ion peak of $(C_7H_6Cl)^+$ at m/z 125, 127. The CI mass spectrum of the trimethylsilyl derivative of metabolite G displayed a quasimolecular ion of $(M + H)^+$ at m/z 328, 330 (3:1 ratio). The ^1H NMR spectrum of metabolite G (Figure 1) showed a three-proton singlet at δ 1.22 instead of a six-proton singlet normally observed for the *gem*-dimethyl group of the parent compound at δ 1.27, indicating disappearance of one methyl group from the *gem*-dimethyl system. Appearance of an AB quartet at δ 3.51–3.77, characteristic of a CH_2OH function, suggested that one of the two methyl groups had been hydroxylated. Additional resonance of a second AB quartet at δ 4.06–4.50 of CH_2ON system, which was originally detected as a singlet in the parent compound, suggests an alteration at C4 in metabolite G,

resulting in a chiral center. Indeed, the C4 position in the parent compound is a prochiral center, and modification of a methyl group on C4 would induce such chirality. The resulted chirality of C4 in metabolite G rendered the CH_2-OH and CH_2ON protons magnetically nonequivalent, therefore generating the two aforementioned AB quartet systems. The resonance at δ 7.41 (complex m, $CH_2C_6H_4$-Cl, 4 aromatic protons) confirmed that the aromatic moiety was intact. This proved unequivocally the structure of metabolite G as (hydroxymethyl)clomazone.

DISCUSSION

Extraction and fractionation of the radioactive residues of clomazone in soybean plant tissues at 30 and 60 days after planting showed similar distributions of the nonconjugated metabolites, conjugated metabolites, and bound residues (Table I). The fraction containing nonconjugated metabolites accounted for a low percentage ranging between 2.9% and 7.9%. The majority of residues was extracted as conjugated metabolites (77.7–81.4%, Table I). Most of each conjugated metabolite fraction (>85%) was susceptible to cellulase hydrolysis, suggesting a high level of glycosidic conjugation of clomazone metabolites in soybean. Based on the metabolite profile, proposed pathways of clomazone metabolism in soybeans are shown in Figure 2. The fact that 2-chlorobenzyl alcohol was the major metabolite (36.9–44.0% of total radiocarbon) suggests that N-dealkylation is a major metabolic process in the metabolism of clomazone in plants. This metabolic process appears similar to the N-dealkylation of dialkylamide herbicides such as diphenamid and napropamid occurring in plants (Ashton and Crafts, 1981). In the case of clomazone, oxidative dealkylation may have resulted in formation of 2-chlorobenzaldehyde, which was either further oxidized to 2-chlorobenzoic acid or reduced to 2-chlorobenzyl alcohol. Ikeda et al. (1986a,b) showed that 2-chlorobenzyl alcohol glycoside is a substantial metabolite conjugate in the metabolism of the 2-chlorobenzyl-substituted herbicide orbenocarb in cotton.

Monohydroxylation of the parent compound to hydroxyclomazone(s) followed by conversion to their glycoside conjugates is another metabolic route (metabolites E–G). This metabolic route contributed up to 17.2–17.4% of the total extractable radiocarbon. It is also likely that 5-hydroxyclomazone (metabolite E) was further oxidized to 5-ketoclomazone (metabolite A). It is important to mention that, although the actual species responsible for the herbicidal activity of clomazone is still unknown, 5-ketoclomazone has been shown to be herbicidally active and may indeed contribute to clomazone's overall herbicidal potency (Chang et al., 1987). Furthermore, it is interesting that 5-ketoclomazone is isolated from the conjugated metabolite fraction, although it contains no conventional conjugation functionality. A possible explanation might be that in a biological system 5-ketoclomazone would be hydrolyzed to its hydroxy acid by esterases (Figure 2), followed by glycosylation to its corresponding glycoside(s). In a workup procedure the eventual enzymatic hydrolysis of the formed glycoside(s) using glycosidases would give back the hydroxy acid, which under low pH conditions would lactonize back to 5-ketoclomazone. This process is analogous to that observed in the rat metabolism of clomazone (Wu et al., 1983), where a hydroxy acid glucuronide conjugate was found to lactonize to form 5-ketoclomazone following enzymatic hydrolysis.

ABBREVIATIONS USED

ai/ha, active ingredient per hectare; LSC, liquid scintillation counter; HPLC, high-performance liquid chromatography; TLC, thin-layer chromatography; v/v, volume per volume; Waters HPLC curve 4 is a convex gradient used in Waters software and solvent programmers; UV, ultraviolet; GC, gas chromatography; FID, flame ionization detector; EI, electron impact; CI, chemical ionization; MS, mass spectrometry; TMS, tetramethylsilane; NMR, nuclear magnetic resonance; RP, reversed phase; i.d., inside diameter; cv., cultivar; TRR, total radiocarbon residue. All solvents used were of Baker Analyzed HPLC reagent grade.

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Registry No. Clomazone, 81777-89-1; 5-ketoclomazone, 80959-17-7; 2-chlorobenzyl alcohol, 17849-38-6; 5-hydroxyclomazone, 81778-16-7; 5′-hydroxyclomazone, 140225-78-1; (hydroxymethyl)-clomazone, 140360-36-7.