Read

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APR 8 1994

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

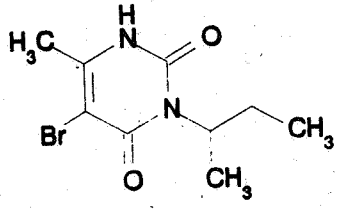
SUBJECT: Bromacil. Case No. 0041. Goat Metabolism. MRID No. 42998901. CBRS No. 12949. DP Barcode:D197454.

FROM: Leung Cheng, Chemist
Special Review Section I
Chemistry Branch II - Reregistration Support
Health Effects Division (7509C)

THROUGH: Andrew R. Rathman, Section Head
Special Review Section I
Chemistry Branch II - Reregistration Support
Health Effects Division (7509C)

TO: Mario Fiol, CRM 73
Reregistration Branch
Special Review/Reregistration Division (7508W)

In response to the Bromacil Data Call-In Notice of 9/91, Dupont Agricultural Products has submitted a study entitled "Metabolism of [^{14}C]-Bromacil by Lactating Goats", Report No. AMR 2283-92. Bromacil is 5-bromo-3-sec-butyl-6-methyluracil. Its structure is shown below.



Chemical Number: 012301

The Product and Residue Chemistry chapters for the bromacil Second Round Review (SRR) were issued 8/15/89. Tolerances for residues of bromacil are established at 0.1 ppm only in/on citrus and pineapples [40 CFR 180.210].

CONCLUSION AND RECOMMENDATION

The metabolism of bromacil in the goat is adequately understood. Bromacil was hydroxylated at the 6-methyl and the sec-butyl side chains. The 6-hydroxymethyl derivative was further conjugated.

Since there are currently no crops registered that may be fed to poultry, a poultry metabolism study is not required (8/15/89 Bromacil SRR). GLN 171-4(b) is satisfied for reregistration.

Results of the current goat study show a maximum transfer of radioactivity in milk (0.04 ppm) when the goat was dosed with bromacil at 9.2 ppm in its diet. The maximum residue (activity) in tissues was 0.02 ppm in kidney. Assuming a 33% dried citrus pulp in the cattle diet and thus a dietary burden of 0.033 ppm, total residues of bromacil that may transfer to meat and milk would be <0.0001 ppm, a level that would not be quantitated by the current analytical methods. Therefore, conventional feeding studies and animal tolerances are not needed.

Detailed Considerations

The in-life phase of the study (dosing, sample collection, residue distribution analysis) was performed by ABC Labs, Columbia, MO; the qualitative and quantitative characterization of residues in the excreta, milk, and tissues was conducted at Dupont, Wilmington, DE.

Carbon-14 labeled at the C-2 position of bromacil was used without dilution with cold bromacil. It had a specific activity of 31.33 μCi/mg and a radiochemical purity of >98%. A lactating goat was given bromacil mixed with cellulose (23.12 mg compound/50 mg cellulose) in a capsule for 3 consecutive mornings after the morning milking (4/28 - 4/30/92). Based on a feed intake of 2.5 Kg, the dose was equivalent to 9.2 ppm (approximately a 280x dosing level). A control goat was also included in the study. The goats were sacrificed on 5/1/92 and all samples of tissue were collected within 24 hours of the last dose. Tissues collected included blood, omental fat, perirenal fat, kidney, liver, muscles, rumen and intestine with contents, and gall bladder contents.

Morning milk and milk from the previous afternoon were mixed to yield a composite sample. Muscle, kidney and liver samples were ground in a Hobart food grinder. Equal amounts (729 g) of each muscle type - longissimus dorsi, semimembranosus and triceps - were ground together to form a composite sample. Equal amounts (250 g) of omental and perirenal fat were mixed to form a composite sample. Samples were ground with dry ice and then samples were stored in a freezer. A subsample from each composite was removed for

radioanalysis. All samples were stored frozen at about -20 C until shipment to Dupont.

For radioanalysis, activity in milk (five samples) and urine were determined by scintillation counting. Samples of feces, muscle, liver, blood, and kidney were combusted before counting. Fat samples were solubilized for radioanalysis. Levels of bromacil equivalents were 0.038-0.040 ppm in milk (3 days), 0.011 ppm in liver, 0.016 ppm in kidney, 0.002 ppm in composite muscle, and 0.002 ppm in composite fat. About 88.5% of the administered dose was recovered in urine and feces (88.9% total recovery).

Residues in tissues were analyzed by HPLC (radiochemical detector and UV detector set at 280 nm) and peak comparison with reference standards: bromacil, 5-bromo-6-methyluracil (IN-T83), 5-bromo-3-(3-hydroxy-1-methylpropyl)-6-methyluracil (IN-JV522), 5-bromo-3-(2-hydroxy-1-methylpropyl)-6-methyluracil (IN-JY141: d,l-erythro or IN-W1380:d,l-threo), 5-bromo-3-(1-hydroxymethylpropyl)-6-methyluracil (IN-D1810), 3-sec-butyl-6-methyluracil (IN-N975), and 5-bromo-3-sec-butyl-6-hydroxymethyluracil (IN-G1088).

The identity of bromacil as one of the metabolites in milk was achieved by HPLC, TLC, and GC/MS analyses. Two milk metabolites were tentatively determined as being derived from hydroxylation of the butyl side chain. One other component was found to be inert towards glusulase.

Residue characterization and identification in milk, liver and kidney are tabulated in Table 1.

Table 1. Distribution and Characterization/Identification of Radioactive Residues in Milk, Liver and Kidney of Goat Fed 9.2 ppm of Carbon-14 Bromacil for 3 Consecutive Days.

Fraction	% TRR	ppm	Characterization/identification
Milk		0.04	
extractable	95	0.039	parent was the major component (0.0073 ppm); 4 unknowns (0.0075, 0.0035, 0.0047, 0.0018 ppm), two of which were hydroxylated at the sec-butyl side chain, one was inert to glusulase
residue	5.3	0.002	not analyzed (N/A)
Liver		0.011	

Fraction	% TRR	ppm	Characterization/identification
extractable	62	0.008	parent was the major component (<0.004 ppm) with a small amount of sec-butyl hydroxylation products
residue		0.005	N/A
Kidney		0.016	
extractable	86	0.013	bromacil and sec-butyl hydroxylation products (<0.01 ppm)
residue	14	0.002	N/A

Several metabolites in the urine were also identified. Two major peaks U1 (51% TRR) and U2 (12%) were isolated after preparative HPLC. For U1, the mass spectroscopic data: M-1 m/z 355/357, M-SO_3H m/z 275/277 and pmr data agreed with the sulfate conjugate of 6-hydroxymethyl bromacil (IN-G1088). U1 upon treatment with glusulase gradually decreased in concentration along with the appearance of 6-hydroxymethyl bromacil, providing further evidence for its identity. U2 was found to consist of two compounds, IN-JV522 and IN-JY141, and identified by HPLC co-injection and HPLC/MS with the respective reference standards.

The registrant proposed a pathway in which bromacil was hydroxylated at the 6-methyl and the sec-butyl side chains. The 6-hydroxymethyl derivative was further conjugated.

CBRS concludes that very low levels of bromacil residues were transferred to milk, muscle, fat, liver and kidney. The primary route of elimination of bromacil was through excretion (urine and feces). The registrant has provided adequate characterization and identification for this study.

cc:Circ, SF, RF, Reg Std File, Cheng
RDI:ARathman:4/5/94:MMetzger:4/5/94:EZager:4/6/94
7509C:CBRS:LCheng:CM#2:RM804/810D:3/31/94:03:a:\BROMACIL\GOATMETA