

September 6, 1978

For Reference

9-6-78

Metabolism of metolachlor: re: TOX memo of 8/23/78. (PP#'s 5G1553, 5F1606, 6G1708, 7F1913, 8F2081, 8F2098)

FROM: Donald Reed & William Boodee, Chemists
Residue Chemistry Branch, HED (TS-769)

TO: Toxicology Branch (Attn: D. Ritter)
Hazard Evaluation Division (TS-769)
and

✓ H. Jacoby, PM #24
HFB/RD (TS-767)

J. Skaptason, Acting Chief
Branch #5/SPRD (TS-791)

THRU: Chief, Residue Chemistry Branch *YAC*

TOX has postulated in the memorandum of 8/23/78 that monochloroacetic acid may be present in food as a metabolite of metolachlor; this compound is considered to be of significant toxicological concern. Mr. Ritter has noted that the difference between the parent compound and CGA-37913, the major compound formed and determined by the analytical method, is the monochloroacetyl (MCA) moiety. (See Figure 1, which was included in our review of PP# 7F1913, D. Reed, 6/14/77). CGA-37913 is not a major plant or animal metabolite of metolachlor; it is formed when conjugated metabolites of the general structure shown in Figure 1 are subjected to refluxing with strong HCl. Thus, rather stringent hydrolysis conditions appear to be necessary to form CGA-37913. Furthermore, the plant metabolism studies generally indicate that dechlorination of the parent compound is one of the first steps in the metabolic process, preceding or occurring simultaneously with the conjugate formation. This is well illustrated in Ciba-Geigy's proposed metabolism in corn diagram (Figure 3 attached).

There is no evidence in the plant or animal metabolism studies which indicates that CGA-37913 is formed directly, thereby allowing the release of the intact MCA moiety. Such a pathway, if it exists, is therefore minor, and would not be expected to lead to detectable residues of MCA from these uses where the major residues of metolachlor are in the 0.1 ppm range.

Ciba-Geigy was contacted by telephone to determine if they had any additional information, not previously submitted, regarding the potential for residues of MCA on crops from the use of metolachlor. Mr. R. T. Murphy has responded in the attached letter of 9/1/78 to Mr. Cummings. In addition to the points we have cited above, Ciba-Geigy also points out that (a) the amide bond in metolachlor is extremely stable; the steric hindrance encountered because of the ring substitution and the secondary carbon attached to the amide-nitrogen inhibits access to the carbonyl group by all hydrolytic species,

especially the enzymatic catalysts of biological systems; and (b) if hydrolysis of the amide occurred in the metabolism studies with metolachlor, an acid and a radiolabeled secondary amine (a basic compound) would result; since no significant quantities of basic metabolites were found in any plant metabolism study, no chloroacids are to be expected.

Although there are no data directly ruling out the presence of MCA, the available metabolism data and rational theoretical predictions all refute the postulation that MCA would be formed.

The possibility of nitrosoamine formation in the metabolism of metolachlor has also been raised orally by Mr. Cox of SPRD. The above cited evidence, indicating the unlikelihood of forming a free amine such as CGA-37913, also indicate the unlikelihood of subsequently forming a nitrosoamine. Furthermore, the concept of requiring nitrosoamine metabolism data for any pesticide which may metabolize to give a secondary or tertiary amine would be a major new policy which would affect dozens, or even hundreds, of pesticides. Instituting such a requirement requires addressing major problems of method feasibility, and should only be made policy upon the recommendation of the Nitrosoamine Panel.

Conclusions and Recommendations.

We do not consider additional data necessary to rule out the postulated occurrence of detectable residues of MCA (or nitrosoamines formed by metabolism) in connection with the low level tolerances for residues of metolachlor on soybeans, corn, meat, milk and eggs.

If any future uses of metolachlor are proposed, which lead to high residues on direct human food items, more specific data on the presence of MCA may be required. This will depend upon what is indicated by the basic plant metabolism studies on the subject crop. Should direct data on the possible presence of MCA be deemed necessary in such a case, we would recommend a radiolabeled metabolism study (^{14}C in the carbonyl position) on the subject crop to determine if a minor metabolic pathway leading to residues of MCA does exist.

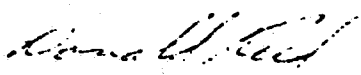
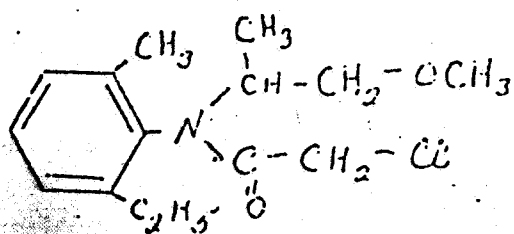
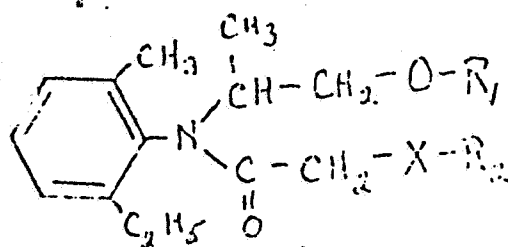

Donald Reed

Figure 1: Metolachlor Alteration



CGA-24705
(Metolachlor)

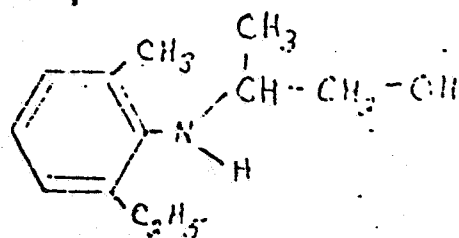
PLANT METABOLISM



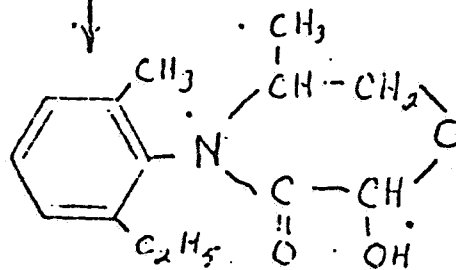
Where: R_1 & R_2 = methyl group
or a natural product moiety
(i.e. amino acids, sugars
or sugar acids)

$X = O$ or S

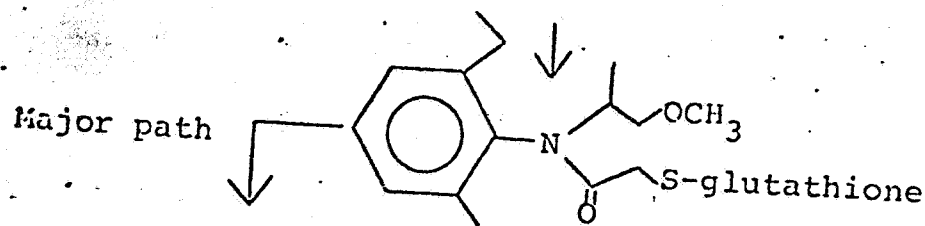
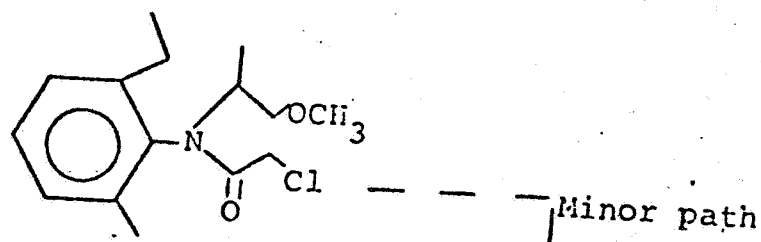
METHOD CONVERSION
(Refluxing with HCl)



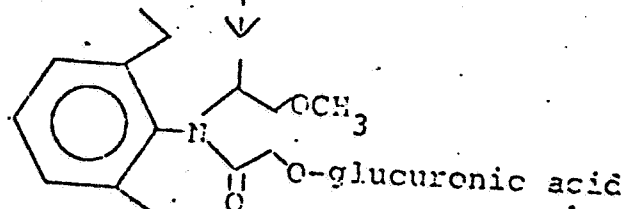
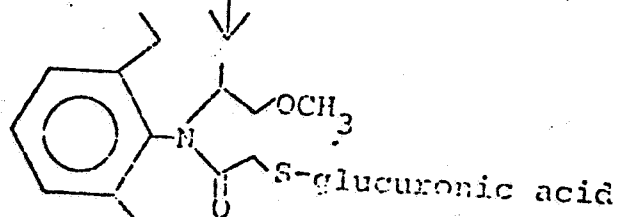
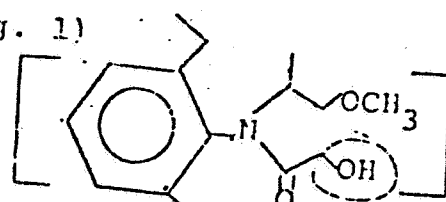
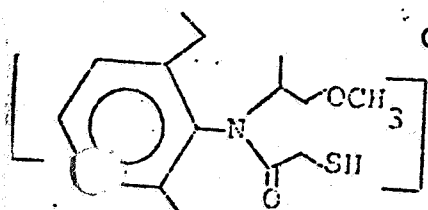
CGA-37913
2-((2-ethyl-6-methyl-
phenyl)amino)-1-propanol



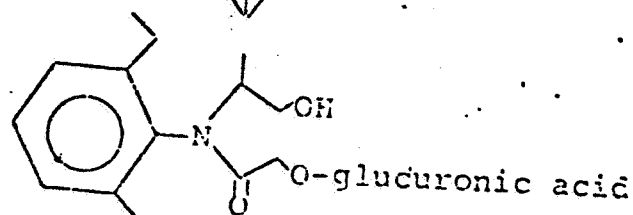
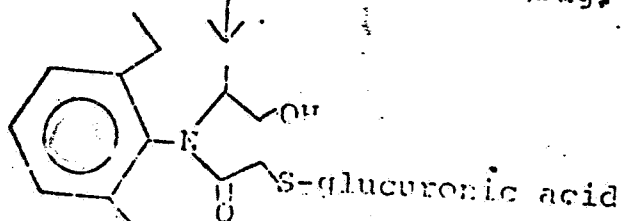
CGA-49751
4-(2-ethyl-6-methylphenyl)-
2-hydroxy-5-methyl-
3-morpholinone



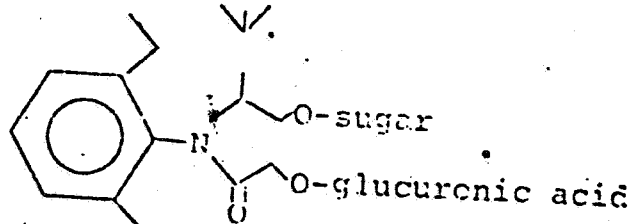
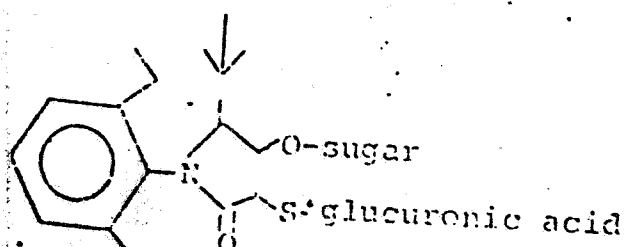
Compound M (Fig. 1)



Zone 6, Compound N (Fig. 1)



Zone 4



Zone 3, Compound O (Fig. 1)