ATTACHMENT N

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

8/23/85

OFFICE OF
PESTICIDES AND TOXIC SUBSTA

MEMORANDUM

SUBJECT: Structural Similarity of ACETOCHLOR To Other Positive Oncogens

FROM: W. Teeters, Pharmacologist w/ Teeters 8-23-85
Acting Head, Section V
Toxicology Branch (TS-769C)

TO: Reto Engler, Ph.D.
Chief, Scientific Mission Support Staff
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On the following page are the chemical structures of ACETOCHLOR and several close analogues (taken from a memorandum of July 29, 1983 to R. Taylor from A. Mahfouz). All are substituted chloroacetanilides excepts Allidochlor, which is a chloroacetamide. Metolachlor is produced by Ciba-Geigy; the others are all Monsanto products.

ACETOCHLOR is a positive carcinogen which induces an increased incidence of liver carcinomas and thyroid follicular cell adenomas in male rats (5000 ppm) and there was a positive trend for hepatic carcinomas in females. In mice at doses of 500, 1500 and 5000 ppm, there were increased incidences of liver carcinomas in high level males, total lung tumors in females of all levels, carcinomas of the lungs in low and high level females, uterine histiocytic sarcomas in females of all levels and total benign ovarian tumors in mid-level females. There were positive linear trends for: liver carcinomas in both sexes, and pulmonary carcinomas, total lung tumors, ovarian benign tumors and kidney adenomas in females (memorandum of August 5, 1985 to R. Taylor from W. Teeters).

Additionally, ACETOCHLOR was weekly positive in the CHO/HGPRT gene mutation assay at near toxic doses but the vehicle used (alcohol) had some activity. It was also positive (with activation only) in the mouse lymphoma test. Negative results were obtained in the Ames salmonella test and in two tests which were unacceptable: the bone marrow chromosome aberration and hepatocyte DNA repair tests.

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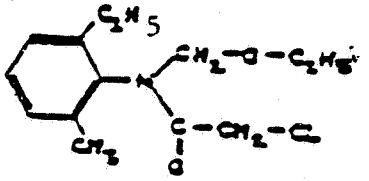

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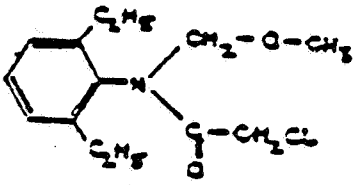
Acetochlor



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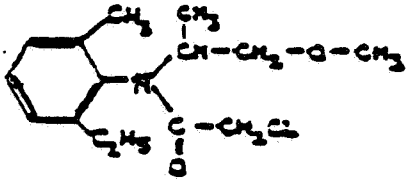
Alachlor



Metolachlor

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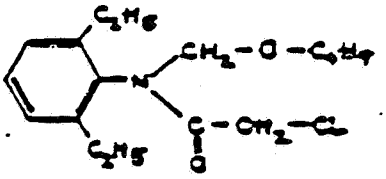

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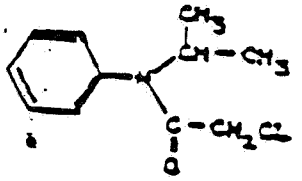
Butachlor



Propachlor

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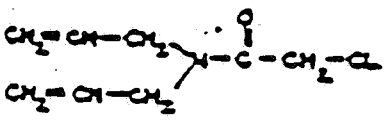

Allidochlor

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The rat teratology study with ACETOCHLOR was negative at a dose of 400 mg/kg, and the rabbit study must be repeated.

Decreased numbers of pups/litter were seen at a dose of 5000 ppm in a rat reproductive study with ACETOCHLOR.

ALACHLOR is also oncogenic in both rats and mice. In rats, it caused nasal turbinate (42 mg/kg) and stomach tumors (126 mg/kg) in both sexes and thyroid follicular adenomas in males (146 mg/kg). In mice, there was an increased incidence of lung tumors in females (260 mg/kg). (See memorandum of 6-16-82 to R. Taylor from A. Mahfouz).

BUTACHLOR (Machete™) causes stomach tumors (only defined as masses at necropsy) in female rats (3000 ppm). (See memorandum of 1-4-83 to R. Taylor from W. Dykstra.)

METOLACHLOR caused a significantly elevated incidence of proliferative liver lesions (neoplastic nodules plus carcinomas combined) at the highest dose level tested (3000 ppm) in female rats. The mouse oncogenic study was negative for proliferative lesions. (See "Peer Review of Metolachlor".)

PROPACHLOR (Ramrod™) and ALLIDOCHLOR (Randox™) were both tested by Industrial Bio-Test Laboratories and these long term studies must be repeated.

cc: Acetochlor File, Caswell #3B