

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

SUBJECT: Metolachlor Evaluation

DATE: January 26, 1978

FROM: Pharmacologist, Metabolic Effects Branch

TO: Mr. James Skaptason,
Metolachlor Team Leader

I have attached the data evaluations (revised) and summaries for the following:

1. Acute Oral in Rats and Dogs
2. Acute Dermal
3. Skin Irritation
4. Eye Irritation
5. Skin Sensitization by Two Methods
6. Subacute Oral Toxicity in Dogs
7. Teratology
8. Mutagenicity by Two Different Protocols

Since Dr. Gross has been on travel this week, I have not turned in a revised acute inhalation evaluation or summary. I think these reports will be sufficient to use as examples of the system. Mr. Chitlik will give you an evaluation and summary of the subacute oral in rats, although I have not looked it over.

Two major studies which haven't begun to be reviewed are the oncogenic study in mice and a three-generation study in rats. Judging from my quick review of the reproduc-

tion summary, this will take a lot of time and probably conferences with CIBA-GEIGY in addition to a redo of the statistics. Mr. Chitlik has the oncogenic study.

WJB
William Burnam

Attachment

cc: Dr. Lamar B. Dale, Jr.
Mr. W. Thomas Edwards
Ms. Carolyn Gregorio
Mr. Larry Chitlik

Acute Oral Toxicity

Summary

Only one available study estimated an acute oral LD₅₀ for technical metolachlor. This was the rat study by Bathe, R. (1973) for CIBA-GEIGY. This material was found to be emetic to dogs (Affiliated Medical Research, 1974).

The LD₅₀ in rats: 2780 mg/kg (2130-3545)

The emetic dose 50 in dogs: 19.0 mg/kg $\pm$ 9.7.

Class III labeling is required based on acute oral toxicity.

ACUTE DERMAL TOXICITY

SUMMARY

Data on the acute toxicity of technical metolachlor is limited to the work reported by affiliated Medical Research, Incorporated (1974):

<u>Species</u>	<u>LD₅₀</u>
New Zealand Rabbit (unabraded)	Greater than 10,000 mg/kg

The data is acceptable to establish that technical metolachlor is low toxicity to the rabbit when tested by the unabraded dermal route. This information meets the requirements for acute dermal toxicity for the unabraded rabbit skin.

Additional data should be required to establish the acute dermal toxicity for abraded rabbit skin.

Based on the available information for this data requirement, technical metolachlor should be placed into Toxicity Category III.

PRIMARY EYE IRRITATION

SUMMARY

Data on primary eye irritation of technical metolachlor is limited to the work reported by Sachsse, K. (1973):

<u>Species</u>	<u>Formulation</u>	<u>Eye Irritation Index</u>
New Zealand Rabbit	Technical (0.1 ml)	0 for cornea; 0 for iris, 0 for conjunctivae

The data is acceptable to establish that technical metolachlor is non-irritating the eye of rabbits. This study meets the requirement for primary eye irritation in rabbits.

Based on the available information for this data requirement, technical metolachlor should be placed in Toxicity Category IV [no eye irritation].

PRIMARY DERMAL IRRITATION

SUMMARY

Data on primary dermal irritation of technical metolachlor is limited to the work reported by Sachsse, K. (1973):

<u>Species</u>	<u>Technical Metalachlor</u>	<u>Primary Irritation Index</u>
New Zealand Rabbit	0.5 ml	0.1

The data is acceptable to establish that technical metolachlor is non-irritating to rabbit skin. This information meets the requirements for primary dermal irritation of rabbit skin.

Based on the available information for this data requirement, technical metolachlor should be placed in Toxicity Category IV [mild or slight irritation at 72 hours].

Dermal Sensitization

Summary

Data on dermal sensitization of technical metolachlor are reported by:

1. Affiliated Medical Research, Incorporated (1974). This study used the closed patch method. Technical metolachlor or chloro-nitrobenzene (considered positive control) were applied to the unabraded skin of Hartley Guinea Pigs. No positive reaction was exhibited by either group. The study does not satisfy requirements for dermal sensitization, since the test system did not respond to the positive control.
2. Sachsse and Ullman (1977). This study used the intradermal injection method: Technical metolachlor dissolved in vehicle [propylene glycol] or vehicle alone [negative control] were intradermally injected into the skin of Pilbright Guinea Pigs. Positive reaction was demonstrated in animals injected with technical metolachlor dissolved in vehicle; no reaction in animals injected with the vehicle alone. This study does satisfy requirements for dermal sensitization, since the test system responded to the expected negative control.

Based on the above information, technical metolachlor is a skin sensitizer in guinea pigs, and this fact should be reflected on the precautionary label and patterns of use.

SUBACUTE ORAL TOXICITY

SUMMARY

Data on subacute oral toxicity of technical metholachlor includes the work reported by The Oncins Research and Breeding Center, Report IC.DRES 740120, March 1, 1974:

Species

Rat

Observed No Effect Level

1000 ppm after 13 weeks
in diet

Unanswered questions still persist as to reported pathology principally noted in the respiratory tract and evident in control as well as test animals. These questions can be resolved by requesting more precise description of these lesions from the laboratory pathologist. It is also recommended that an EPA pathologist review the pathology reports on individual animals in this study.

Until questions pertaining to the pathology in this study are answered, (see review) this study cannot fulfill regulatory requirements. It should be recognized, however, that chronic feeding studies should resolve any questions pertaining to the toxicity of metolachlor.

Dog Subacute Feeding Study

Summary

Data on the subacute toxicity of metolachlor dogs is limited to that supplied by Coquet, B. et al., (1974). We reviewed the English translation supplied to us by CIBA-GEIGY Corp.

At the highest dose levels used, 150 (i.e., 4-5 mg/kg per day) and 500 ppm (i.e., 14-19 mg/kg per day) administered over a period of 15 weeks and also 1000 ppm (27-36 mg/kg per day) administered over a period of seven consecutive weeks, no animals died and there were found no manifestly toxic effects which could be attributed to metolachlor.

A suggestion of decreased weight change at higher dose level may have been due to impalatability.

The presence of excessive pulmonary lesions raises some doubt concerning the adequacy of controls. These lesions were similar in kinds, numbers and severity to those found in treated animals. This study should be considered acceptable unless or until treatment related pulmonary lesions are found in the forthcoming 2-year study in rats.

Teratogenic Study

Summary

The only teratogenic study on metolachlor was by Fritz (1976). The study found that doses of either 0, 60, 180 or 360 mg/kg/day during days 6 to 15 of gestation were without effect to the offspring of female Sprague-Dawley rats. No fetotoxic or teratogenic effects of the compound were observed. The only possible effect on the dams was a decrease in food consumption at the highest dose during the first 1/3 of the experiment.

This study meets current requirements for teratogenic study in one species and based on this study, metolachlor does not present a teratogenic hazard. Current requirements call for two teratogenic studies in mammals and the registrant should be advised that an additional study will be needed.

MUTAGENICITY

SUMMARY

Citations which were considered were the following:

- 1) Arnie, P., Muller; D., (1976) Salmonella/Mammalian Microsome Mutagenicity Test with CGA-24705 (Unpublished report prepared by CIBA-GEIGY Ltd.)
- 2) Fritz, H. (1976). Dominant Lethal Study on CGA-24705 Technical --Mouse (Unpublished report prepared by CIBA-GEIGY Ltd.)

Potential of metolachlor to cause genetic changes was tested for by two test systems--a bacterial system utilizing activation by mammalian microsomes, and an in vivo system to test the effect on developing sperm in the mouse.

The Salmonella system tested for base substitutions and point mutations at various ranges (10,100, 1,000 and 10,000 ug/plate). No increases in background mutation rates were observed.

Neither were there any effects noted on fertility rates or zygote or embryo death in the mice after single oral doses of 100 or 300 mg/kg. Malformations of resulting embryos were not reported.

From these two studies, no evidence is presented which suggests that metolachlor has any mutagenic potential.

These two test systems satisfy proposed guidelines for the testing requirements for mutagenic potential for the present, although in the future, additional studies may be required.