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EFFECTS ASSESSMENT - HUMANS AND DOMESTIC ANIMALS

## TOXICITY TO LABORATORY ANIMALS

### Acute Oral Toxicity (Section 162.81-1)

The minimum data requirement for acute oral testing is one test on the laboratory rat.

The acute oral $LD_{50}$ in the laboratory rat was 2780 mg/kg with 95% confidence limits of 2130-3545 mg/kg (Bathe, 1973).

Technical metolachlor in corn oil has been shown to be emetic in beagle dogs to an extent that precludes the establishment of an oral $LD_{50}$ in dogs (Affiliated Medical Research, 1974). The study did, however, establish the emetic $dose_{50}$ to be 19.0 mg/kg $\pm$ 9.7.

On the basis of acute oral toxicity category III labeling is required for technical metolachlor.

The above information is sufficient to satisfy the requirement for acute oral toxicity on technical metolachlor.

### Acute Dermal Toxicity (Section 162.81-2)

The minimum data requirement for acute dermal testing is one test preferably on the albino rabbit. This test must be conducted on both intact and abraded skin.

Affiliated Medical Research, Incorporated (1974) established that the $LD_{50}$ to the New Zealand rabbit is greater than 10,000 mg/kg when tested by the unabraded dermal route.

No data is available on the acute dermal toxicity to abraded rabbit skin. This data is required and is discussed further in the portion of the technical metolachlor standard dealing with data gaps (see page ).

Based on the available information on acute dermal toxicity, category III toxicity labeling is required for technical metolachlor.

The above information is sufficient to meet the requirement for acute dermal toxicity testing on intact skin for technical metolachlor.

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Acute Inhalation Toxicity 162.81-3

The minimum requirement for acute inhalation is one test conducted in one mammalian species (the albino rat is the animal of choice).

The acute inhalation toxicity is limited to the work done by Sachsse (1974):

| Species | Duration | $LC_{50}$ |
|---|---|---|
| Rat | 4 hr./exposure | >1.752 mg/l (no deaths at this maximum achievable level) |

Based on this inhalation study a category II labeling should be required for technical metolachlor. This study meets the requirement for acute inhalation toxicity on metolachlor.

Primary Eye Irritation (Section 162.81-4)

The minimum data requirement for the eye irritation is one test conducted on the albino rabbit.

A study of eye irritation was conducted by Sachsse (1973) on the New Zealand rabbit. In that study 0.1 ml of technical metolachlor was used. The test was evaluated using the system of Draize (1959) and produced the following eye irritation indices at 24 hours and 7 days.

Cornea: 0
Iris: 0
Conjunctivae: 0

This study establishes that technical metolachlor is nonirritating to the rabbit eye and, therefore, toxicity category IV labeling is required with regard to eye irritation.

The above information is sufficient to meet the requirement for primary eye irritation data for technical metolachor.

Primary Dermal Irritation (Section 162.81-5)

The minimum data requirement for primary dermal irritation is one test conducted on a mammal, preferably the albino rabbit.

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Sachsse (1973) evaluated the dermal irritation of technical metolachlor on the New Zealand rabbit. In that study, 0.5 ml of technical metolachlor was used. The test was evaluated using the system of Draize (1959) and resulted in a primary irritation index of 0.1 [highest possible score is 8.0].

This information establishes that technical metolachlor is nonirritating to rabbit skin; therefore, toxicity category IV labeling is required with regard to dermal irritation.

The above information is sufficient to meet the requirement for primary dermal irritation data for technical metolachlor.

Dermal Sensitization (Section 162.81-6)

The minimum data requirement for dermal sensitization is a patch or intradermal test on one mammalian species, preferably the male albino guinea pig.

The first evaluation of dermal sensitization was conducted by Affiliated Medical Research, Incorporated (1974). The lack of sensitization in a positive control invalidated this study and precludes its use in the regulatory process.

A second study (Sachsse and Ullman, 1977) used the intradermal injection method. Technical metolachlor dissolved in the vehicle [propylene glycol] or the 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 the vehicle; no reaction in animals injected with the vehicle alone.

Based on this study, technical metolachlor is a skin sensitizer in guinea pigs.

This information is sufficient to meet the requirement for dermal sensitization data on technical metolachlor.

Acute Delayed Neurotoxicity Study (Section 162.81-8)

It is required to support registration if the active ingredient(s), or any of its(their) metabolites, degradation products, or impurities cause esterase depression or are structurally related to a substance that induces this specific neuropathy or delayed neurotoxicity.

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Metolachlor is a chloroacetanilide herbicide and we would not expect this chemical to cause esterase depression that induces delayed neurotoxicity. This data is not required for technical metolachlor.

Subchronic Oral (Section 162.82-1)

Rat Study

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

| Species | Observed No Effect Level |
|---|---|
| Rat | 1000 ppm after 13 weeks in diet |

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.

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

Dog Study

Four male and four female beagles were fed the following diets:

(1) 0 ppm (Control)
(2) 50 ppm metolachlor for 8 weeks, 1000 ppm for 7 weeks
(3) 150 ppm metolachlor for 15 weeks
(4) 500 ppm metolachlor for 15 weeks

No compound - related effects were noted with regard to mortality, signs of toxicity, organ weights, body weights, gross and histopathology. None of the doses caused any toxic effects. At the end of the study, all dogs including control had bacterial or viral infections.

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Due to the lack of any effects, i.e. the dose was not high enough, and due to the ill health of the dogs, this study is not acceptable for a non-rodent subacute feeding study. A six month feeding study in dogs using effect and no effect level doses is required.

The minimum data requirement for sub-chronic oral testing is one study in two mammalian species one of which must be the rat and the other a non-rodent preferably the dog.

Subchronic 21-day dermal (162.82-2)

The minimum data requirement is one study in one mammalian species. Data on the subacute dermal toxicity of Metolachlor-6E is reported by Affiliated Medical Research, Incorporated (1974).

The data is acceptable to establish that Metolachlor-6E is moderately irritating when applied to the skin at both dose levels and causes decreased body weight gains at the high level (75% solution 6E), but was not evidenced at the low dose level (37.5% solution 6E).

This information meets the requirements for subacute dermal toxicity.

Subchronic 90-day Dermal Toxicity Study

This study is not required since the existing pattern of metolachlor use preplanting and premergence would not result in repeated human skin contact.

Subchronic Inhalation Toxicity 162.82-4

The use should not result in repeated inhalation exposure at a concentration which is likely to be toxic as determined by acute inhalation test.

Subchronic Neurotoxicity Studies (162.82-5)

Metolachlor is a chlorocetanilide and is related to registered chemicals similar in structure that "have not induced neuropathy or delayed neurotoxicity, as evidenced by the results of an acute test".

Not required for technical metolachlor.

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Chronic Feeding Study (162.83-1)

In progress.

Oncogenicity (162.83-2)

Summary

At this time oncogenicity data on technical Metolachlor is limited to the study done by Industrial Bio-Test Laboratories, Inc., Report No. 622-07925, December 15, 1977:

| Species | Dose levels & Conclusion |
|---|---|
| Charles River CD-1 Albino Mice | Not oncogenic when fed at dietary levels of 0, 30, 1000 and 3000 ppm for 18 months to males and 20 months to females. |

The study, as submitted, has a number of shortcomings. Essentially these relate to poor reporting of (1) actual test procedure, (2) actual observations, and (3) unexpected problems which developed during the conduct of this study. This study report is misleading as well as incomplete and must be revised to accurately reflect the conduct of this study.

The histopathology data, on the other hand, appears complete and has been validated by Ciba-Geigy. This histopathology data revealed that Metolachlor did not induce an increase in neoplastic or non-neoplastic lesions when fed to Charles River CD-1 mice at levels of 0, 30, 1000 and 3000 ppm.

There are indications that animals husbandry was far from ideal during the conduct of this study and that this contributed to the reduced longevity and body weights of these mice (e.g. - males were sacrificed several months earlier than females to insure adequate numbers for examination).

The study was audited by Ciba-Geigy and stated to be valid. It appears that their primary concern in this audit was the pathology data, but their attention should have been given to the entire conduct of the study.

If and/or when the revised report is submitted reevaluation may be necessary, but at this time the pathology data supports the report conclusions regarding oncogenicity.

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Teratogenicity (162.83-3)

The minimun data requirement for teratology is testing in two mammalian species.

The data on teratology is limited to work reported by Fritz (1976).

| Species | Results |
|---|---|
| Sprague-Dawley rat | No teratogenic effect observed at doses up to 360 mg/kg/day during 6-15 days gestation. |

The study determined 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 which may indicate that this was the beginning of toxic maternal doses.

No data is available on a second mammalian species. This data is required and is discussed further in the portion of the technical metolachlor standard dealing with data gaps (see page ).

Based on the available teratology data it does not appear that metalochlor presents a teratogenic hazard.

The above study is sufficient to meet the requirement for teratology in one species of mammal.

Reproduction (Section 162.83-4)

The minimum data requirement for measuring reproductive induces in one mammalian species is limited to the work done by Smith and Adler (1973):

Smith and Adler (1973) fed a diet containing up to 1000 ppm which did not affect reproduction during a three generation (2 litters per generation) reproductive study in the rat.

This data is sufficient to meet the requirement for a multigeneration reproductive study.

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Mutagenicity Testing (Section (162.84-1)

The minimum data requirements for mutagenicity is testing in two systems.

The potential of metolachlor to cause genetic changes has been tested for in two test systems--a bacterial system utilizing activation by mammalian microsomes (Arnie and Muller, 1976), and an in vivo system to test the effect on developing sperm in the mouse (Fritz, 1976).

The bacterial (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 studies are sufficient to meet the present requirements for mutagenicity testing.

## HUMAN EFFECTS FIELD STUDIES

No accident information or any other information with regard to human effects of metolachlor have been reported.

## SIGNS AND PATHOLOGY IN MAMMALS

Orally, metolachlor produced sedation, dyspnea, exophthalmus, curved position, trismus, tonic-clonic muscle spasms and ruffled for within two hours post intubation. Additionally, an emetic doses of 19 mg/kg was observed in dogs.

Intradermal injection produced sensitization in guinea pigs.

No pathology was observed in test animals which was chemical related.

## HUMAN EFFECTS ASSESSMENT

No human effects have been reported.

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Control

## SUMMARY OF EXPECTED HUMAN EFFECTS

We have no data on metolachlor with regard to its effects on humans. The below statements only reflect what might reasonably be expected, for man, based upon the extrapolation of animal data to man.

Based on the data, emesis and skin sensitization would be expected. These signs observed in animals have not been reported as yet in formulators or applicators.

No pathology associated with the chemical has been identified.

## DATA GAPS

Acute dermal $LD_{50}$ - abraded skin.

Subchronic oral feeding study in 2 species.

Teratogenicity - mammal other than rat.

Chronic toxicity study in the rat.

## LABELING REQUIREMENTS

The statement "Harmful if swallowed" is based on the acute oral $LD_{50}$ 2780 mg/kg with 95% confidence limits of 2180-3545 mg/kg.

The statements "May be fatal in inhaled. Do not breathe vapors", are based on the inhalation toxicity study by Sachsse K. et al (1974) where the $LC_{50}$ is assumed to be higher than 1752 mg/cu. m. Over 65% of the particles measured were greater than 7 microms.

The study by Sachsse and Ullman, 1977, demonstrated that metolachlor is a sensitizer when injected intradermally to guinea pigs. The following statements should appear on the label:

"This chemical may cause allergic reaction. Avoid contact with skin and clothing. Flush exposed skin with water."

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## TOXICITY TO DOMESTIC ANIMALS

The acute oral $LD_{50}$ on dogs was not determined due to an emetic effect. An emetic $dose_{50}$ of 19.0 mg/kg $\pm$ 9.7 mg/kg was established.

There are no field studies.

## DOMESTIC ANIMALS EFFECT ASSESSMENT

The likelihood of exposure of domestic animals to this technical product would be minimal if any.

## SUMMARY OF EXPECTED DOMESTIC ANIMALS EFFECTS

The emetic $dose_{50}$ of 19.0 mg/kg $\pm$ 9.7 mg/kg was established for the dog. No data available on the chronic effect. The likelihood of chronic exposure of domestic animals to this chemical would be minimal if any.