5-3-78

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

000434

DATE: May 3, 1978

SUBJECT: Substantive Amendment to PP No. 7F1913 proposing a tolerance of 0.1 ppm for the herbicide metolachlor and its metabolites in or on soybeans and 0.02 ppm in eggs, milk, and the meat, fat of cattle, goats, hogs, horses, poultry and sheep.

FROM: Laurence D. Chitlik, Toxicologist LDC
Toxicology Branch, RD (WH-567)

TO: Henry M. Jacoby, PM #24
Registration Division (WH-567)

Petitioner: Ciba-Geigy Corporation

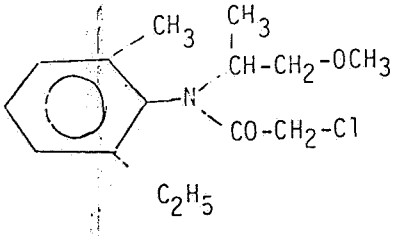
Pesticide Petition: 7F1913

Common Name: Metolachlor (formerly CGA-24705)

Product Name: Dual (R) 6E

Chemical Name: 2-Chloro-N-(2-ethyl-6-methylphenyl)-N-(2-methoxy-1-methylethyl)acetamide

Structural Formula:



Proposed Tolerance: (1) 0.1 ppm in or on soybeans
(2) 0.02 ppm meat, milk and eggs

Existing Tolerances: (1) Temporary tolerance on soybeans at .1 ppm and forage and hay at 1.25 ppm
(2) 0.1 ppm corn grain

Related Petitions: 5G1553, 5F1606, 6G1708

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MRID 00015396

EPA FORM 1320-6 (REV. 3-7...

Metabolites: 2-[(2-ethyl-6-methylphenyl)amino]-1 propanol and 4-[2-ethyl-6-methylphenyl]-2-hydroxy-5-methyl-3-morpholinone

RECOMMENDATIONS:

Toxicology data submitted in the substantive amendment of 1/17/78, PP No. 7F1913, (proposing a tolerance for the herbicide, metolachlor and its metabolites at 0.1 ppm in or on soybeans and 0.02 ppm in eggs, milk and the meat, fat of cattle, goats, hogs, horses, poultry and sheep) are insufficient for a human health hazard assessment.

The following deficiencies are noted:

1. A second oncogenic study must be submitted.

2. Two chronic feeding studies must be submitted.

3. Deficiencies noted in the mouse oncogenic study, IBT No. 622-07925 (8532-07925), 12/15/77 must be corrected in the revised report. See review attached.

4. Deficiencies noted in the rat 90-day feeding study must be corrected. (Oncins Research and Breeding Center, Report IC-DREB-R 740120, 3/1/74). See review attached.

5. Deficiencies in the Dog, 90-Day feeding study must be corrected and/or a new study should be submitted.

TOX Branch has been informed that a Metolachlor Rat Chronic feeding study with oncogenic evaluation has been recently completed by Industrial Bio-Test Laboratories, that it is presently revising this study, and that it may now be submitted to the agency in the very near future. (Personal communication from Dr. D. Sumner of Ciba-Geigy to L. Chitlik of TOX Branch). Upon receipt of and satisfactory review of this study, TOX Branch may be able to act favorably in this action, if Ciba-Geigy agrees to correct the TOX data deficiencies (noted in this review and attachments) in a very timely fashion. TOX Branch agrees to expeditiously review the rat chronic feeding study when it is finally submitted. We find that although available metolachlor data indicates a relatively low toxicity of this chemical, data are insufficient at this time for a favorable recommendation.

BACKGROUND:

PP No. 7F1913 was originally reviewed by D.L. Ritter, 3/31/77, and the proposed 0.1 ppm tolerance for metolachlor and its metabolites was denied because of insufficient toxicity data. The amendment of 8/1/77 was also reviewed by D.L. Ritter, 9/19/77, and toxicology data deficiencies were essentially the same as the original review. Data gaps included a completed two-year rat feeding study, a mouse oncogenicity study, a second chronic feeding/oncogenicity study, a multigeneration reproduction study, a mutagenicity assay using a mammalian test system, "analytical data of the rat teratology study", metabolism studies designed to elucidate excretion patterns and animal metabolites."

The CHM review of 6/14/77, D. Reed, concluded that this new use in soybeans would be expected to result in some human exposure to residues of metolachlor. The amendment of 8/1/77, included revised sections B and F, adding (1) the restriction, "Do not graze or feed soybean hay or forage treated with Dual 6E alone or tank mixtures containing Dual 6E." and (2) a tolerance proposal at 0.02 ppm in eggs, milk, and the meat, fat of cattle, goats, hogs, horses, poultry and sheep. These revised sections B and F satisfied deficiencies noted in the chemistry review of 6/14/77.

Animal metabolism studies have been reviewed in conjunction with PP #1553 (see review of D. Reed, 6/14/77, PP #7F1913). These studies in rats and goats using ^{14}C-labeled metolachlor and in goats only using ^{14}C-corn biosynthesized metabolites "show rapid elimination with only trace levels in liver. Furthermore, be noted that the hydrolyzed pesticide moieties are similar in plants and ruminants and concluded that the metabolism of metolachlor in animals is adequately defined.

REVIEW:

The substantive amendment to PP #7F1913 (1/17/78) contained a number of newly submitted studies which in part satisfy the TOX data deficiencies noted in the reviews of D.L. Ritter, 3/31/77 and 9/19/77. The studies submitted in this amendment were reviewed with the generic standard format and summaries of these reviews follow:

1. Rat, Teratogenicity Study, CGA-24705 technical, Indentified as a "Reproduction Study, Seg. II", Ciba-Geigy Limited, Experiment No. 227625, 6/21/76 (with Addendum).

   Reviewed by W.L. Burnam, 1/23/78.

Conclusions:

Doses of up to 360 mg/kg/day during days 6-15 of gestation had no adverse effect (either fetotoxic or teratogenic) on the offspring.

Note: What is Seg. I of this study?
This study is classified as core minimum data.

See review attached.

2. Mouse, Dominant Lethal, CGA-24705, Identified as "Cytotoxic or mutagenic effects on male germinal cells", PH 2.632, Ciba-Geigy Ltd., 9/8/76, with addendum.

Reviewed by Christine F. Chaisson, 1/26/78.

Conclusions:

No genetic changes were induced in mice after an acute oral exposure. No effects on the male germ cells (from A-spermatogonia to mature sperm) could be seen, as measured by fertility or zygote death.

This study is classified as core minimum data.

See review attached.

3. Guinea Pig, Skin Sensitization, Identified as "Skin Sensitizing (Contact allergenic) Effect in Guinea Pigs of Technical CGA-24705", Ciba-Geigy Ltd., PH 2.635, 10/17/77.

Reviewed by Carolyn Gregorio, 1/24/78.

Conclusions:

Technical metolachlor is a skin sensitizer in albino guinea pigs. A positive reaction was noted in 16/20 tested. This study is classified as core minimum data.

See review attached.

4. Rat, Three-Generation Reproduction Study, CGA-24705 Technical, IBT No. 8533-07928, 1/4/78 and Ciba-Geigy Audit Report, 1/12/78.

Reviewed by William L. Burnam, 2/27/78.

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Conclusions:

No adverse effects on any reproductive indices could be attributed to the pesticide metolachlor when fed at levels of 30, 300 or 1000ppm. Reduced fertility noted at the low dose (30 ppm) of the F_2a in males and females is not dose related and thus does not constitute a significant adverse effect. Likewise, the reduced percent of parturition at the low dose of the F_3a and F does not appear significant since at the highest dose the incidence of parturition was 100% for both the F_3a and F_{3b} litters.

This study is classified as core minimum data.

See complete review attached.

5. Mouse, Carcinogenicity Study, (males 18 month, and females 20 months) CGA-24705 Technical, Industrial Bio-Test, IBT No. 622-07925 (8532-07925), 12/15/77 and Ciba-Geigy Audit Report of 1/12/78.

Reviewed by L.D. Chitlik, 3/1/78.

Conclusions:

The test report is misleading and incomplete and must be revised to accurately reflect the conduct of this study. Actual procedure, observations and unexpected problems which developed during the study are either absent from or incorrect in the report as submitted.

Metolachlor did not appear to 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, however, re-evaluation may be necessary when a revised report is submitted.

See complete review attached.

In addition to the studies submitted in this amendment to PP No. 1913, the following studies were also considered in this action:

1. Rat, 90-Day Feeding Study, Technical Metolchlor, the Oncins Research and Breeding Center, Report IC-DREB-R 740 120, 3/1/74; Received originally under PP No. 5G1553.

Reviewed originally by R.B. Jaeger under PP No. 5G1553, 11/12/74, but also reviewed for the Metolachlor Standard by L.D. Chitlik, 1/25/78 and Eleanor L. Long, 3/14/78, with "Summary", 4/14/78.

Conclusions:

Although submitted data indicates an observed "NEL" of 1000 ppm in rats fed for 13 weeks, pathology data is incomplete and possibly inaccurate. A number of questions exist concerning pathologic changes in the lungs (alveolar wall thickening, hemorrhage and hemorrhagic alveolitis) and slides of lung tissue must be reviewed by a second pathologist. Also the full complement of tissues from the high dose level, group III (1000 ppm for 10 weeks followed by 2000 ppm for weeks 11 through 13) must be examined and results submitted. Likewise, any gross lesions from the T-II animals should have been microscopically examined.

Without answers to the questions raised and the requested data, it is not appropriate at this time for final determination of the observed "NEL".

See attached review.

2. Dog, 90-Day Feeding Study, CGA-24705 Technical, Oncins Research and Breeding Center, Report IC-DREB-R 740119, 1974, Received under PP No. 5G1553.

Initially reviewed by R.B. Jaeger, 11/12/74, under PP No. 5G1553 but also reviewed by Thomas Edwards for the Metolachlor Standard.

Conclusions:

In telephone conversation with T. Edwards, 5/2/78, it was indicated that this study was "not acceptable" and that an EPA pathologist has been requested to review the pathology data. The concerns in this study relate to possible similarities between lung pathology in this study and the rat 90-day feeding study.

Note: Review not attached.

R/D Init: GEWhitmore 5/3/78

LDChitlik/ccw

For GEW 5/4/78

4/14/78

000434

SUBACUTE ORAL TOXICITY

SUMMARY

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

In the review of 1/25/78, a number of questions were raised concerning the pathology data submitted in this study. It was recommended, at that time, that an EPA pathologist review this pathology data. This review was completed by Dr. Eleanor L. Long, M.D., Pathologist, on 3/14/78. Dr. Long found a number of the same types of deficiencies previously noted in the pathology data and raised still other questions about this data.

These questions must be resolved before this study is used to fulfill any further regulatory requirements. Although available data indicates an observed "NEL" of 1000 ppm (fed for 13 weeks), the pathology data has been found to be incomplete and inaccurate. Until all of the following questions and/or deficiencies are resolved, final determination of an observed "NEL" would not be appropriate:

1. The following questions concerning pathologic changes in the lungs must be answered:

   a. The nature and cause of the alleged alveolar wall thickening.

   b. The nature, incidence, and cause of hemorrhage and hemorrhagic alveolitis.

2. The slides of the lungs, from this 90-day rat study must be reviewed by a second pathologist.

3. The full complement of tissues from the rats in the high dose level, group III (1000 ppm for 10 weeks followed by 2000 ppm for weeks 11 through 13, males 321-330 and females 351-360) must be examined and results submitted.

4. Dr. Long noted that T-II animals were not examined. Considering that long-term rodent studies are being conducted, heart, liver, kidneys, and lungs do not necessarily have to be examined for this study to be accepted for tolerance setting purposes. However, any gross lesions from this group should have been examined and results submitted for review.

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NOTE: Dr. Long's reference to the "standard" in her review was referring to the proposed Guideline requirement standards.

Laurence D. Chitlik

Laurence D. Chitlik
Toxicology Branch
Registration Division (WH-567)

DATA EVALUATION RECORD 000434

1. CHEMICAL: Metolachlor (CGA 24705)

2. FORMULATION: Technical Grade P7, dried

3. CITATION: Coquet, B.; Galland, L.; Guyot, D.; Fouillet, X.; Rouaud, J.L. (1974) Three-Month Oral Toxicity Trial of CGA 24 705 in Rats. A translation of: Essai de Toxicite de 3 Mois Chez le Rat par Voie Orale du Produit CGA 24 705: IC-DREB-R 740120. Received Mar. 1, 1974 under 5G1553. (Unpublished report prepared by the Oncins Research and Breeding Center for CIBA-GEIGY Corp., Greensboro, N.C.: CDL:94219-A).

4. TRADE SECRET CLAIM: Yes

5. REASON FOR REVIEW: Generic Standard for Metolachlor

6. REVIEWED BY: Laurence D. Chitlik
Toxicologist, Toxicology Branch
Registration Division

7. DATE OF REVIEW: January 25, 1978

8. TEST TYPE: Subacute Oral Study

A. Materials and Methods: Sprague-Dawley OF A rats bred and raised at Oncins Breeding Center under "specific pathogen-free conditions" were used in this study. At the start of the study they were 4-5 weeks of age and assigned to 4 groups as follows:

	No. of Animals	Dose Level
Controls	30 males, 30 females	0 ppm
Group I	20 " 20 "	100 ppm
Group II	20 " 20 "	300 ppm
Group III	30 " 30 "	1000 ppm

No toxic manifestations were evident in any group at week ten. It was then decided to increase the dose of Group I rats from 100 ppm to 2000 ppm for the remaining 3 weeks of the study. Ten rats per sex from Group III (1000 ppm) also received increased levels of 2000 ppm for the remaining 3 weeks of study and then were sacrificed after a recovery period of 4 weeks (week 17).

The diet was prepared by diluting CGA 24 705 with 95% ethanol and mixing it at a rate of 2 ml per kg of feed (powdered feed, IFFARAT) in a preliminary and final blend. Residues of ethanol were considered negligible. Feed was offered ad libitum.

The animals were housed 5 to a cage with sterilized sawdust bedding. Air was recirculated 8 times per hour.

Hematology, blood chemistry, urinalysis, body weight, and food consumption values were determined.

At necropsy, liver, kidney, adrenal, gonad, brain and spleen weights were determined from all animals. Tissues from these organs as well as optic nerve, eye, thyroid, thymus, small intestine, colon, pancreas, trachea, lung, aorta, striated muscle, bladder, seminal vesicle, prostate or uterus, heart, lymph ganglia and pituitary were subjected to microscopic examination.

Each test parameter was analyzed to find means and standard deviations. Student's t test was used for comparisons between groups (D. Schwartz, Statistical Methods Used by Physicians and Biologists, Flammarion, 1963).

B. Reported Results: No deviations in relation to behavior, ocular examination, mean body weights, food intake and hematology were reported.

At 4 weeks, slight deviations of glycemia were noted in animals of the 300 and 1000 ppm groups, but this was not considered "pathologic" and control levels were even higher at 8 weeks. At 8 weeks, a slight drop of alkaline phosphatase in the 3 treatment groups and again in the highest two groups at 13 weeks were noted. This slight decrease was within normal limits.

Urinalysis revealed no unusual findings with the exception of (1) At 4 weeks, traces of glucose and ketone bodies in one female of Group II (2) At 13 weeks, traces of glucose in five males and two females of Group III (1000 ppm) and traces of bile pigments in one male of Group III.

Necropsy revealed very few lesions (pg. 126 of the report) and these were not considered significant.

Statistical evaluation of absolute and relative organ weights revealed the following:

1. Group I female rats (100 ppm elevated to 2000 ppm) showed increased liver weights, both absolute (10% difference stated) and relative.

2. Female rats of Group II (300 ppm) and Group III (2000 ppm) showed no significant variations.

3. Group I male rats (100 ppm)elevated to 2000 ppm showed no difference.

4. Group II male rats had slightly decreased liver weights, both absolute and relative.

5. Group III males (1000 ppm) showed no significant variation from controls.

The report concluded on this point that the 10% difference in Group I females is not of significance.

Conclusions reached after histopathology examination indicated that there was no evidence of a compound related effect at any level.

The pathologist, X. Fouillet, stated that lesions were essentially found in the respiratory tract and that these were caused by the diet powder which irritated the mucous membrane or by the anesthesia used before sacrifice, resulting in edema of the tunica propria (corium) and detachment of the epithelium in the trachea.

In the lungs of control and test group animals, hemorrhagic alveolitis, thickening of the alveolar walls, bronchiolectasis and peribronchial lymphoid infiltrates were noted. The hemorrhagic alveolitis was explained to "probably" be caused by decapitation of the animals while the other lesions "may have been caused by inhalation of the alimentary powder deposited in the cages, or by viral infection."

The pathologist concluded that all lesions observed were "not related to the compound." He therefore implied that the highest

test level 100 ppm for 10 weeks (in the diet) and 2000 ppm for 3 weeks (in the diet) was a no effect level.

An addendum to this report was submitted in conjunction with PP No. 1605. It included histopathology data on Group III (1000 ppm for 13 weeks) as well as data on 3 control rats not included in the original submission.

The pathologist stated that the small lymphoid foci in the liver, and the unobstructive tubular nephrosis in the kidneys with proteic casts are findings common in Sprague-Dawley OF A rats. He also repeated his conclusions of the original report and conceded that thickening of the alveolar walls may be of infectious origin. He also found no significant difference between lesions in the control and test groups and concluded the observed no effect level would be 1000 ppm.

C. Discussion: This reviewer concurs that the kidney lesions found in these rats are common to Sprague-Dawley rats and therefore it can be concluded that they are not compound related, especially since they occurred in both control and treated animals.

The lesions of the respiratory tract (with the exception of hemorrhagic alveolitis which may be due to decapitation) ~~is~~ are more difficult to understand. The lesions described occur in both control and test animals yet they are not common lesions to expect. Thickening of the alveolar walls is suggestive of infection, and/or it is compound related. It is not a normally expected lesion in control animals raised under "Specific Pathogen-Free Conditions", even though in this study it is very evident. Bronchiolectasis, would also not be expected in control animals. The pathologist, X. Fouillet, concluded that bronchiolectasis, peribronchial lymphoid infiltrates, as well as edema of the tunica propria and detachment of the epithelium in the trachea was due to either (1) inhalation of the diet powder or (2) infection. The fact that the diet may have been air-borne and inhaled is very suggestive that contamination of control animals occurred. Furthermore, if this did occur, the value of controls for purposes of comparison to the test groups is impossible. If the second possibility, that is infection is the case, valid compound effects can still be very difficult to discern.

D. Conclusions: Considering that lesions occurred in both control and test animals at similar frequencies, it can be concluded that the observed no effect level is 1000 ppm (fed for 13 weeks). Considering the questions relating to the pathology in this study, the following recommendations are also made.

1. An EPA pathologist should review the pathology in this study.

2. The laboratory pathologist who read the slides should be requested to give more precise explanations.

3. The lesions noted in this study should be checked for carefully in the chronic studies submitted on Metolachlor. Long term feeding studies should provide the needed answers to these questions.

000434

March 14, 1978

TO: Mr. Lawrence Chitlik
Toxicologist, TOX

FROM: Eleanor L. Long, M.D.
Pathologist, TOX

SUBJECT: Metolachlor (CGA-24705). 90-Day Rat Feeding Study.

Pesticide Petition 5G1553

In regard to your question as to whether the pathological work-up on this study is good enough for the study to serve as a standard, after reviewing it, it is my opinion that certain questions concerning it need to be answered first.

Group	Rats Begun	Rat Numbers	PPM Diet Weeks 1-10	PPM Diet Weeks 11-13	Number Microsectioned
Controls (T)					
Males	30	1-30	0	0	20 (1-20)
Females	30	31-60	0	0	20 (31-50)
I					
Males	20	101-120	100	2000	20 (101-120)
Females	20	121-140	100	2000	20 (121-140)
II					
Males	20	201-220	300	?300	0
Females	20	221-240	300	?300	0
III					
Males	30	301-320	1000	1000	20 (301-320)
		321-330	1000	2000	0
Females	30	331-350	1000	1000	20 (331-350)
		351-360	1000	2000	0

Questions and Discussion

1. Microscopic Examination.

a. Why were the rats which received the highest dose, i.e., Group III, 1000 ppm for the first 10 weeks followed by 2000 for the last 3 (weeks 11 through 13) not studied microscopically? According to the company's report there is no evidence that these animals (males 321-330 and females 351-360) were so studied, although the other animals in Group III, i.e., those which received 1000 ppm for the entire 13-week period, were examined microscopically. If these highest dose animals have not been so studied, a complete histopathologic work-up on them will be necessary.

b. Another defect in the microscopic examination is the apparent failure to so examine any organs from the middle dose (Group II, 300 ppm) animals, as the proposed Guidelines now require histopathologic study of liver, kidney, heart, any gross lesion, and any target organ on all rats at the low and intermediate levels. Provided longterm rodent studies have been done on this compound, as I understand is the case, this deficiency in the subchronic rat study should not affect tolerance-setting, but the study cannot be considered standard as long as this particular deficiency exists.

1.1

2. Lungs.

a. One change, peribronchial lymphocytic infiltration, is normal in all rats.

b. I suspect hemorrhage and hemorrhagic alveolitis are one and the same, as there is no"hemorrhage" described in the animals originally submitted (Controls and GRoup I) though 9/20 male controls, 7/20 female controls, and 6/20 males and 6/20 females in Group 1 (100 ppm increased to 2000) show "hemorrhagic alveolitis", and, conversely, in the animals submitted later, Group III, none of the rats is described as having "hemorrhagic alveolitis" whereas 4/20 males and 8/20 females are said to show simple "hemorrhage". This suggests that 2 pathologists were involved, though it is later stated that there was only one. Simple hemorrhage can easily be attributed to terminal aspiration of blood when the throats were cut at decapitation, as the company suggests, and would be expected in all groups, as appears to be the case. If there were no associated leukocytic infiltration (inflammatory cells), and none is described [except for a single female control with interstitial pneumonia, 3 rats with rare foci of foamy macrophages (2 controls and 1 Group I female), and possibly a total of 3 (1 male control, 1 Group I male, and 1 Group I female) with bronchiectasis (which properly consists of inflammation and other changes in addition to dilatation of bronchi and bronchioles)], the term "alveolitis" is incorrect. This terminology may, of course, reflect a less than accurate translation from French to English. All in all, I suspect that simple "hemorrhage", which cannot be ascribed to the compound tested, rather than "hemorrhagic alveolitis" is present in these rats.

c. What was the cause of thickening of the alveolar walls? This is definitely abnormal. If compound-induced, it is indeed serious. Also, as it is approximately equally distributed through all groups, occurring in 1/3 to ½ the animals, the suspicion has arisen that inhalation due to cross contamination might explain its presence in the controls. Another suggested etiology is infection, which can be ruled out because of the virtual absence of inflammatory cells, as was discussed in the preceding paragraph; even in old rats chronic pulmonary infections, including the very rare healed ones, are characterized by the presence of inflammatory cells in addition to fibrosis and other changes, and these animals are only 3-months old. This absence of leukocytes, particularly macrophages, also makes it highly unlikely that the thickening can be attributed to inhalation of the test compound. There are 2 other possible explanations. (1) Overreading of the slides by an inexperienced pathologist. (2) Thick sections cut on the microtome by a poor technician; this implies that the apparently normal lungs were cut by a second technician. It is important that the cause of this alveolar wall thickening, whether real or not, be established. In regard to this particular study, the opinion of a second pathologist would be helpful. For regulatory purposes, absence of similar changes in the chronic rat toxicity study would strongly suggest that the changes in the present subacute study are artefact or not really present.

3. Trachea.

Edema of the tunica (lamina) propria and detachment of the epithelium are described in almost every rat and attributed to other anesthesia. This is possible, especially if accompanied by traumatic handling. In any event, these changes cannot be ascribed to administration of Metolachlor

[redacted]

4. Other Organs.

A small amount of cast formation primarily located at the cortico-medullary junction is described in the kidneys of 1/3 to ½ the animals in all groups, including the controls. As there is no more in treated than in control groups, this cannot be attributed to the compound fed and no doubt represents early onset of the progressive glomerulonephritis seen in all strains of rats and known to appear at an unusually early age in the Sprague-Dawley strains such as this one(Sprague-Dawley OFA). Other lesions, such as hydronephrosis and gastric junctional acanthosis

(the latter to some extent normal), are reported in a few animals from all groups, and are no doubt spontaneous lesions common in the strain and in no way associated with the pesticide which was fed.

SUMMARY

There are 2 major questions concerning pathologic changes in the lungs of these Sprague-Dawley OFA rats in this subchronic, 90-day feeding study on Metolachlor which should be answered before tolerances are set: (1) the nature and cause of the alleged alveolar wall thickening, and (2) the nature, incidence, and cause of hemorrhage and hemorrhagic alveolitis. While these problems may be resolved by the findings in the longterm rat study, better descriptions of the lesions seen and review of the microslides of the lungs by a second pathologist are recommended. If the study is also to serve as a standard, in addition to solving these problems two other deficiencies in the histopathologic examination, namely, the failure to examine microscopically (1) the full complement of organs from the rats in Group III given the highest dose (those given 1000 ppm for 10 weeks followed by 2000 ppm for weeks 11 through 13) and (2) the heart, liver, kidneys, lungs, and any gross lesions from the rats on the intermediate dose (Group II), should first be corrected.

ONCOGENICITY

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 Ceiba-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 animal 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 ensure adequate numbers for examination).

The study was audited by Ceiba-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.

Lawrence D. Chitlik

1. CHEMICAL: Metolachlor (CGA24705)

2. FORMULATION: CGA-24705 Technical (FL-750227 99.9% active and FL-752105 96.5% active)

3. CITATION: Gesme, J.; Albanese E.,; Marias, A.J.; Arces, R.J. (December 15, 1977) Carcinogenicity Study with CGA-24705 Technical in Albino Mice: IBT No. 622-07925 (8532-07925). Received January 18, 1978 under 7F1913. (Unpublished report prepared by Industrial Bio-Test Laboratories, Inc. for CIBA-GEIGY Corp., Greensboro, N.C.: CDL: 096719

4. TRADE SECRET CLAIM: Yes

5. REASON FOR REVIEW: Generic Standard for Metolachlor

6. REVIEWED BY: Laurence D. Chitlik
Toxicologist, Toxicology Branch
Registration Division

7. DATE OF REVIEW: March 1, 1978

8. TEST TYPE: Oncogenicity

A. Materials and Methods: Four hundred (200 males and 200 females) Charles River CD-1 Albino mice aged 35-40 days were received, observed for an additional 7 day period and then assigned to 4 groups as follows:

Group	Dietary level in PPM	Number of Animals Males	Females
Control	0	50	50
T-I	30	50	50
T-II	1,000	50	50
T-III	3,000	50	50

Males were housed in individual cages while females were housed 5 to a cage. Cages were identified by color-coded cards identifying the project number, dietary level, animal number and sex. Individual animals were identified with ear tags. Observations for toxic signs and/or death were conducted twice

daily. Necropsies were conducted on all animals found dead (unless autolyzed), sacrificed *in extremis*, and sacrificed at term. Tissues were fixed in 10% neutral buffered formalin. The following tissues were prepared for microscopic examinations (stained with Hematoxylin-Eosin) and examined (from all animals, except autolyzed):

Adrenal Glands
Aorta (thoracic segment)
Brain (cerebrum, cerebellum, pons)
Caecum
Colon
Epididymis
Esophagus
Eyes with optic nerve
Gonads
Heart
Kidneys
Liver
Lung
Lymph Nodes (cervical, mesenteric)
Mammary Gland
Muscle (skeletal)
ALL NEOPLASMS & SUSPECT NEOPLASMS
Pancreas
Parathyroid Gland
Peripheral Nerve
Pituitary Gland
Prostate Gland
Salivary Gland (submaxillary, sublingual, parotid)
Small Intestine (duodenum, jejunum,
Spinal Cord
Spleen
Sternum with marrow
Stomach (cardia, fundus, pyloris)
Thyroid Glands
Trachea
Urinary bladder
Uterus

Body weight data were requested as an addendum to the protocol after the study was in progress. The first body weights were taken at month 5 and then monthly thereafter.

The test material was mixed with Purina Rat Chow in a high-speed Hobart blender. Test material batch FL-750227 99.9% active ingredient was used during the first 33 weeks while test material batch FL-752105 96.5% A.I. was used for the remainder of the study. The diets were to be corrected for the change in active ingredient. Fresh diets were prepared weekly. Water and diet were to be available *ad libitum* and daily checks were made to ensure this.

Body weight data were statistically analyzed by using a one-way analysis of variance. Any significant body weight effects were then analyzed by either

the Tukey's (equal population size) or the Scheffe's (unequal population size) Multiple Comparison Test. Historical data for mice of this age and strain were also used for the final interpretation of results.

B. REPORTED RESULTS

Average body weights among animals fed 3,000 ppm were slightly lower throughout most of the study as compared to controls. At 1,000 ppm or lower dose levels, body weights were considered comparable to controls, although "meaningful evaluation" could not be determined since body weights were not available during the first 4 months of the study.

No "treatment-related mortalities" were evident, but males were sacrificed at 18 months and females after 20 months to ensure an adequate number of animals at final sacrifice. No unusual behavorial reactions were observed during the study.

Microscopic examinations were conducted by R.J. Arceo, M.D., Staff Pathologist. He concluded that there were no treatment-related morphologic changes. Furthermore, lesions were of a natural origin and occurred with a comparable incidence and relative severity among both control and test animals. The incidence, site of origin and classification of neoplasms compared favorably with historical IBT data for mice of this age and strain. The pathology report indicated that missing tissues (including some thyroids, parathyroids and pituitary) occurred evenly among the test groups and did not interfere with conclusions reached. Some tissues not called for in the protocol (aorta, esophagus, epididymides, seminal vesicles and lacrimal gland) were processed for some animals.

C. DISCUSSION

A number of questions arose during the review of this study and Ciba-Geigy was first contacted 2/8/78, in an effort to resolve them. Other calls followed as new questions developed and Ciba-Geigy submitted

a number of addendums to the study including raw data for observations, and a mouse 28-day range finding study not previously submitted (as well as its audit report).

Originally, one question existed concerning very significant body weight losses in males (especially) and females at month 11 and continuing through month 13. (See GRAPH attached.) The report stated that "No unusual behavioral reactions were observed during the investigation" and also that "Meaningful evaluation of the body weight gain cannot be determined since no body weights were collected during the first four months of the testing." Also, the report did not indicate the strain of mice tested, which was later stated to be Charles River CD-1.

At first Ciba-Geigy (Dr. Rolofson and Dr. Sumner) checked with IBT and could gain no explanation for the weight loss. It was then requested that daily observations data be submitted to Registration Division to determine whether some toxic signs, possible overlooked by IBT, might help explain the weight loss and also demonstrate that dose levels were at an adequate level (Note: The report indicated that the only compound effects were slightly lower average body weights at 3,000 ppm, but also at the same time meaningful evaluation was not possible!).

Ciba-Geigy submitted an addendum to the report dated February 16, 1978. It contained a mouse 28-day range finding study IBT No. 622-07857 (not previously submitted) demonstrating dose levels in this oncogenicity study to be adequate and at or near the MTD. At 10,000 ppm, in this range finding study, moderate weight reduction occurred and no toxic signs were reported.

The addendum also included some discussion by Dr. Darrell Sumner (of Ciba-Geigy) of observations not previously noted in the IBT report. Dr. Sumner stated that no observations were recorded until the 5th month and that dermal lesions were noted at the

eighth month. He also indicated that through much of the study observations were recorded every two weeks rather than twice daily as the test report indicated. It was also explained that allopecia and "eye and ear infections" were common to all groups and tremors, paralysis, distended abdomens, and diarrhea were noted in all groups near the end of the study. He then went on to discuss the weight losses and their significance and commented that the compound does not elicit easily observed toxic signs...

The submission also included a Ciba-Geigy audit report on this study (CGA-24705 range finding study, IBT No. 622-07857, November 21, 1975, dated February 15, 1978).

The discrepancies noted between the report indicating observations were made twice daily versus Ciba-Geigy indicating that they were not made for the first 5 months and after that usually twice per month (but sometimes monthly or sometimes once per week), prompted request of the raw data for the daily observations (received March 9, 1978).

The raw data were reviewed and among other things, the following was noted:

1. At least 10 animals demonstrated dermal lesions as early as July 26, 1976. All of these animals were sacrificed on August 17, 1976 and August 19, 1976 "in extremis."

2. At least 20 animals, 8 T-III males and 9 T-II females exhibited allopecia. At least 6 control animals also demonstrated allopecia.

3. At least 25 test animals and a number of control animals demonstrated "eye irritation."

4. A fair number of test and control animals exhibited equilibrium problems and blood in ear canal.

Several telephone conversations with Dr. Sumner followed review of this data, 3/10/78, and 3/13/78, and an additional submission was received from Ciba-Geigy, 3/15/78 (7 pages).

Mr. Chitlik pointed out to Dr. Sumner that discussion relating to these observations should have been included in the IBT oncogenicity study whether or not IBT toxicologists thought they were compound related. Such determinations have to be made by EPA toxicologists and no mention of any of these or other observations were included in the report submitted to Registration Division.

Mr. Chitlik suggested that the allopecia and "dermal lesions" noted in the study may be related to a mite infestation and inquired as to whether a veterinarian or other IBT staff had made an effort to determine the cause of these observations as well as the eye and ear irritation noted in many animals. In response, the Ciba-Geigy submission of 3/15/78, which includes a memo to Dr. Sumner as well as a number of in-house memos discussing the "daily" observations as well as possible reasons for the body weight losses in both control and test animals.

The memo of A.J. Marias, 3/14/78, indicated the following:

1. The glass jars were replaced by stainless stell feeders in November and December of 1976. Note: This coincides with body weight losses in this study. There was no mention of this in the test report.

2. The feeders did not function properly and had to be modified to allow a greater amount of diet to fill the trough at the bottom of the feeder. Note: There was no mention of this in the test report.

3. The diet was changed during the study from Purina Mouse Chow to Purina Rat Chow. The Purina Rat Chow had a five percent lower fat content. Note: The test report did not indicate a change in diet. It indicates animals were fed Purina Rat Chow only. No date of this change has been indicated by IBT.

4. Marias also stated that during "Animal care meetings" a skin lesion problem, "associated with a number of mouse studies" was discussed and the cause was not readily determined. Dr. Robl was stated to have been unable to observe mites upon microscopic examination on numerous skin scrapings (from this study?) but that mice on related studies revealed the presence of occasional mites associated with the dermatitis.

5. The affected animals were removed from the study and sacrificed in order to avoid spread of the lesion.

   Note: Eleven mice appear to have been sacrificed in the study related to this (Control males 3, 29, 33, 48; T-I male 102; T-II males 222, 226, 227, 230, 247; T-III male 343). They were sacrificed "in extremis" on 8/17/76 and 8/18/76 according to the observations raw data. They are identified as moribunds in the report, yet they were NOT moribund, they were sacrificed to control this problem. The report does not discuss this sacrifice and obviously no discussion of the associated problem is included either.

The memo of A.J. Marias referenced a memo of Dr. Robl (8/18/76). From this memo, the following was determined:

1. Room 9 contained 6 other mouse oncogenic studies, possibly on 6 other compounds.

   Note: The possibility for cross contamination of diet due to such practices is greatly increased. Tremors were noted in all females of groups II and

III on 1/17/77 from 9-10 a.m. This was not noted as occurring at any other time during the study and has so far been unexplained by Ciga-Geigy or IBT. This practice is totally unacceptable according to the proposed GLP's. It may be prudent to determine chemical nature of other compounds run in that room.

2. One study (unidentified) within this room must have had a severe problem and approximately 10 animals in each of the other studies had contracted it... Those 10 animals per study were to be sacrificed.

3. The animals within this study, as well as the others within this room, were to be "rotated into properly cleaned cages as soon as possible." Obviously the animal husbandry was poor.

4. Dr. Robl did not have tissues processed from this other study to determine the cause. He stated that, "Whatever the cause of this problem was, evidently it has been controlled through sacrifice of affected animals."

This reviewer does not believe that if this was a mite infestation, it was controlled by sacrificing these 11 animals. The fairly widespread eye and ear irritation and allopecia which persisted through the study especially in the male animals, is still not completely understood. Possibly the associated dietary and other problems (i.e. difficulties with new feeders) discussed are related to the reduced longevity in this study.

D. CONCLUSIONS

Nearly the entire discussion section of this report relates to poor reporting of data and poor animal husbandry. Some of the findings noted are certainly related to the reduced longevity in this study. These sections of the report should be rewritten by IBT to more accurately reflect the findings in the study.

Review of the histopathology data presented in this study revealed that Metolachlor did not induce any treatment related changes when fed at 0, 30, 1,000, or 3,000 ppm. No increase in either neoplastic or non-neoplastic lesions was noted. A mouse range finding study was conducted which indicated 3,000 ppm at least approaches the MTD even though body weight data and observations within this carcinogenicity study are of little or no use (see DISCUSSION section).

Even with the shortcomings of this study, it is concluded that Metolachlor is not carcinogenic to Charles River CD-1 mice when fed at levels of 30, 1,000 and 3,000 ppm.

This report was audited by D.D. Sumner and R.H. Ross, Jr. of Ciba-Geigy, 1/12/78. An addendum to this audit was submitted 2/16/78. They concluded the study was valid after review of the raw data. Quite a number of deficiencies have been noted in the Ciba-Geigy audit. Nearly all of the findings mentioned in the discussion section of this review were originally omitted from their audit report.

Laurence D Chitlik

Laurence Chitlik
Toxicology Branch

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DATA EVALUATION RECORD

000434

1. CHEMICAL: Metolachlor (108801)

2. FORMULATION: Technical

3. CITATION: CIBA-GEIGY Limited (1976) Dominant Lethal Study on CGA 24705 Technical: Mouse (Test for Cytotoxic or Mutagenic Effects on Male Germinal Cells) PH 2.632. Received January 18, 1978 under 7F1913. (Unpublished report including Addendum; CDL:96717-C; 96717-D)

4 TRADE SECRET CLAIM: Yes

5. REASON FOR REVIEW: Generic Standard for Metolachlor

6. REVIEWED BY: Christine F. Chaisson
Biochemist, Metabolic Effects Branch
Criteria and Evaluation Division

7. DATE OF REVIEW: January 26, 1978

8. TEST TYPE: Cytotoxic or mutagenic effects.

A. Materials and Methods: Male NMRI-derived albino mice were dosed once by intubation with 100 or 300 mg/kg of test substance carried in carboxymethylcellulose. Controls were dosed only with carrier. The males were mated for six weeks with two untreated females per week, which were checked daily for vaginal plugs. At day 14 of pregnancy, females were sacrificed, autopsied and embryos counted. Results were analyzed statistically with the Chi square or Fisher' exact test for comparison of numbers of mated and pregnant dams or embryonic deaths. The T-test or Mann-Whitney's U-test used to compare totals of implantations.

B. Reported Results: After single doses of 100 or 300 mg/kg, no decreased in number of pregnancies per group or mated females were found. There were no effects in numbers of implantations per mating, or numbers of embryonic death.

C. Discussions: The protocol as described is valid, and the statistical evaluations are adequate for the considered parameters. Not discussed however was the apparent decrease in percentage of females mated per male (as noted by vaginal plug). This is not a genetic effect, but may have been due to toxic effects to the male. However no discussion of general health of the male after dosing was mentioned.

There were clearly no effects of the compound on embryonic death, pre- and post- implantation, nor on fertility rates in the mated females. No data was presented, however, on the condition of the resultant embryos. These observations would have been relevant to the question of genetic toxicity of the compound.

D. Conclusions: This study presents valid data to support the view that metolachlor does not induce genetic changes in mice after an acute oral exposure. No effects on the male germ cells (from A-spermatogonia to mature sperm) could be seen, as measured by fertility or zygote death. Malformation of embryo was not considered.

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This test is adequate to meet proposed requirements for the dominant lethal mutagenicity testing.

DATA EVALUATION RECORD

000434

1. CHEMICAL: Metolachlor (108801)

2. FORMULATION: Technical

3. CITATION: Arnie, P; Miller, D. (1976) Salmonella/Mammalian-Microsome Mutagenicity Test with CAG 24705 (Test for Mutagenic Properties in Bacteria): Ph 2.632. Received January 19, 1977 under 7F1913. (Unpublished report prepared by CIBA-GEIGY, Ltd., Basle, Switzerland; CDL:95768-B)

4. TRADE SECRET CLAIM: Yes

5. REASON FOR REVIEW: Generic Standard for Metolachlor

6. REVIEWED BY: Christine F. Chaisson
Biochemist, Metabolic Effects Branch
Criteria and Evaluation Division

7. DATE OF REVIEW: January 12, 1978

8. TEST TYPE: Mutagenicity

A. Materials and Methods: The bacteria Salmonella typhimurium, strains TA-1535, TA-1537, TA-98 and TA-100, were tested for mutagenicity using the Ames Standard Plate Test and Spot Test with and without liver microsomal activation. Levels of 10, 100, 1000 and 10,000 ug/0.1 ml to each plate were used. Significant results were defined as a doubling of the mutation rate above background.

B. Reported Results: In applications of 10, 100, 1000 and 10,000 ug/0.1 ml to each plate, cell death was noted at the highest two levels but no increase over background was observed in reversion to prototrophy. Metolachlor can be considered non-mutagenic in this test system.

C. Discussion: The results are justified.

D. Conclusions: The study indicates that metolachlor, with or without activation is non-mutagenic to four strains of S. typhimurium at all levels tested including toxic levels. The test would meet proposed requirements for one type of mutagenicity testing.

1. Chemical: Metolachlor

2. Formulation: CGA-24705 Technical

3. Citation: Fritz, H. (1976) Reproduction Study CGA-24705 Tech: Rat: II: (Test for Teratogenic or Embryotoxic Effects): PH 2.632. Received January 19, 1977 under 7F1913. (unpublished report prepared by CIBA-GEIGY Ltd., Basle, Switzerland; CDL:95768-A)

4. Reason for Review: Generic Standards for Metolachlor

5. Reviewed by: William L. Burnam
Pharmacologist, Metabolic Effects Branch
Criteria and Evaluation Division

6. Trade Secret Claim: Yes

7. Test Type: Teratogenic Study

A. Test species: Pregnant Sprague-Dawley Rats

B. Reported results: Doses of metolachlor of 0, 60, 180 and 360 mg/kg/day were without effect on the pregnant females and offspring when given orally during a critical period of gestation.

C. Test conditions: Pregnant rats (25 per dose) were intubated from day 6 to day 15 with either 0, 60, 180 or 360 mg/kg/day of compound in 2% CMC. Dams were autopsied on day 21. The viscera and skeletal were examined according to standard procedures. Methods of presenting data were based on numbers of affected fetuses per total number; the litter was not designated as a unit of analysis. Overall, the conduct of the experiment was in keeping with the spirit of EPA guidelines.

D. Statistical Analysis: Statistics were alluded to in the results but except for Table 4, the reviewer could not determine where statistics were used, what type were used and what p value was considered significant.

E. Conclusions: Food consumption for the high dose rats was decreased for the first 1/3 of the experiment; this may indicate the start of the toxic doses However, this decrease was not seen in female body weights nor in mean weights of live fetuses. There were no compound related effects on mean number of implanta-

tions, embryonic resorptions, fetal resorptions, fetal death, or soft tissue or skeletal malformations. Criticisms of the reviewer do not negate this regulatory usefulness of the study.

DATA EVALUATION RECORD

000434

1. CHEMICAL: Metolachlor (103801)

2. FORMULATION: Technical

3. CITATION: Smith, S.H., Adler, C.L. (1978) Final Report to CIBA-GEIGY Corporation: Three-Generation Reproduction Study with CGA-24705 Technical in Albino Rats: IBT No. 8533-07928. Received Jan. 18, 1978 under 7F1913. (Unpublished report prepared by Industrial Bio-Test Laboratories, Inc. for CIBA-GEIGY Corp.; including Audit Report No. 6 prepared by CIBA-GEIGY Corp., Greensboro, N.C.; CDL:96718-A; 96718-B)

4. TRADE SECRET CLAIM: Yes

5. REASON FOR REVIEW: Generic Standard for Metolachlor

6. REVIEWED BY: William L. Burman
Pharmacologist, Metabolic Effects Branch
Criteria and Evaluation Division

7. DATE OF REVIEW: February 27, 1978

8. TEST TYPE: Three-Generation Reproduction

A. Materials and Methods: Weaning CD strain Charles River albino rats (8 males and 16 females per dietary group) were fed either 0, 30, 300 or 1000 ppm technical CGA-24705 in their diet beginning at 22 days of age. The first mating trials were begun when the parental animals were 100 days old. The first litters were weaned at 21 days post-partum sacrified and discarded. After a 10 day rest the parents were mated again. Eight males and 16 females from the second litters were retained to serve as parents of the next generation (F 2). The process was repeated and ended with the weaning of the F2b litters. In the case of the low dose F2b weaning only 13 females are retained due to a lack of animals. Gross and histopathological examinations were carried out on parental rats of all three generations. Gross pathologic examination were conducted on 10 males and 10 females weanings selected at random from the F3b litters of all doses and control. Unless any abnormalities were seen, histopathological studies were carried out on the control and high dose rats only.

Body weights were recorded initially and weekly until mating began. Organ weight of the liver, kidneys, spleen, gonads, heart and brain were recorded and statistically analyzed by analysis of variance. Repulation data, parental and progeny body weight data were analyzed by one way analysis of variance with significant effects checked by Scheffe's multiple comparison tests or by Tukey's Multiple Comparison Test.

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Various indices of reproduction and pup survival which were observed in the study are as follows:

$$\text{Mating Index} = \frac{\text{Number of Copulations*}}{\text{Number of Estrus Cycles Required}} \times 100$$

$$\text{Fecundity Index} = \frac{\text{Number of Pregnancies}}{\text{Number of Copulations}} \times 100$$

$$\text{Male Fertility Index} = \frac{\text{Number of Sires}}{\text{Number of Males Mated with Fertile Females}} \times 100$$

$$\text{Female Fertility Index} = \frac{\text{Number of Pregnancies}}{\text{Number of Females Mated with Fertile Males}} \times 100$$

$$\text{Incidence of Parturition} = \frac{\text{Number of Parturitions}}{\text{Number of Pregnancies}} \times 100$$

$$\text{Live Birth Index} = \frac{\text{Number of Viable Pups Born}}{\text{Total Number of Pups Born}} \times 100$$

$$\text{24-Hour Survival Index} = \frac{\text{Number of Pups Viable at Lactation Day 1}}{\text{Number of Viable Pups Born}} \times 100$$

$$\text{4-Day Survival Index} = \frac{\text{Number of Pups Viable at Lactation Day 4}}{\text{Number of Viable Pups Born}} \times 100$$

$$\text{12-Day Survival Index} = \frac{\text{Number of Pups Viable at Lactation Day 12}}{\text{Number of Pups Retained at Lactation Day 4}} \times 100$$

$$\text{21-Day Survival Index} = \frac{\text{Number of Pups Viable at Weanling (Day 21)}}{\text{Number of Pups Retained at Lactation Day 4}} \times 100$$

*Only 1 copulation counted per estrus cycle. Five days equal 1 estrus cycle.

B. Reported Results: During the F0 and F2 parental generations, males at the high dose had reduced pre-mating body weight gains and final body weights compared to control. When analyzed by analysis of variance these decreased weight gain were not significant. Metolachlor did not affect parental mortality or behavior. Reduced mating indices were observed among the 30 and 1,000 groups during

the F1a litter and among the 30 and 1,000 ppm groups during the F1b litter. Reduced F2a and F3a mating indices were noted among all experimental groups. Reduced fertility was seen during the F2a litters at the low dose. During the F3a and F3b litters there was a decrease in the parturition index at the low dose.

There were no pesticide related effects on the number of pups born and weaned. Progeny survival indices and pup body weights are similar to controls. There were no effects seen on pup development and behavior. Pathological and histopathological examinations revealed no pesticide related changes although mild to moderate chronic murine pneumonia was present in almost every rat sacrificed. Mean organ weights, organ to body ration and organ to brain weight ratios revealed no pesticide related effect.

C. Discussion: Although not statistically significant, there does appear to be a decrease in pre-mating body weight in the F0 parents at the high dose. In the Ciba-Geigy validation, the mating indices were discussed and statistically analyzed at great detail. Based on a Chi-Square Test, significant ($p = 0.05$) variation occurred only in the F3a litter with an almost significant effect in the F2a litter. Linear regression analysis supplied by Ciba-Geigy indicated a good dose-response fit with only F1a, F1b and F2b litters. Historical controls were alluded to in their validation and later sent in Dr. Jack Norton's (Ciba-Geigy), letter of 2/17/78 to Mr. Henry Jacoby EG #24 EPA. These control mating indices from Industrial BIO-TEST's last five reproductive studies place the control mating indices observed in the F3a generation in proper perspective.

Based on these data I consider the unusually high control value in the F3a mating index to be a red herring and should not be considered to indicate that experimental groups were affected adversely by metolachlor.

Reduced fertility noted at the low dose of the F2a in males and females is not dose related and thus does not constitute a significant adverse effect. Likewise the reduced percent of parturition at the low dose of the F3a and F3b litters does not appear significant since at the highest dose the incidence of parturition was 100% for both the F3a and F3b litters.

D. Conclusions: Indices such as the mating index and separate fertility indices for male and female rats are not currently asked for in the Guidelines whereas data on spermatogenesis and additional animals for histopathology which were not in this study are required by the Guidelines. The Guidelines are now stating that only a two-generation study is needed instead of three.

However, the study is adequate to fulfill our requirements for a multi-generation reproductive study. No adverse effects on any reproductive indices could be attributed to the pesticide, metolachlor.

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DATA EVALUATION RECORD

1. CHEMICAL: Metolachlor (108801)

2. FORMULATION: Technical

3. CITATION: Sachsse, K. (1977) Skin Sensitizing (Contact Allergenic) Effect in Guinea Pigs of Technical CGA-24705. Project No. Siss 5726. Received October 17, 1977. [Unpublished Report Prepared by CIBA-GEIGY Ltd., Basle Switzerland].

4. TRADE SECRET CLAIM: Yes

5. REASON FOR REVIEW: Generic Standards for Metolachlor

6. REVIEWED BY: Carolyn Gregorio Carolyn Gregorio
Biochemist, Metabolic Effects Branch
Criteria and Evaluation Division

7. DATE OF REVIEW: January 24, 1978

8. TEST TYPE: Dermal Sensitization Study

A. Materials and Methods: Two groups of twenty [10 males, 10 females] guinea pigs of the Pirbright white strain. The test animals received a total of 10 intracutaneous insult injections [0.1 ml] of freshly prepared 0.1% dilution of technical metolachlor in propylene glycol [test group] or 10 intracutaneous insult injections [0.1 ml] of propylene glycol [control group].

Two weeks following the last insult injection the animals received a challenge injection [0.1 ml] of freshly prepared 0.1% dilution of technical metolachlor in propylene glycol [test group] or propylene glycol [control group].

B. Reported Results: Dermal Reactions after intradermal challenge injection:

Formulation	Treated Animals	Positive Reaction Animals	P value**
Propylene Glycol	20	5	—
Technical + Propylene Glycol	20	16	0.001*

*A probability of 0.01 was considered to indicate a significant difference.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

000434

DATE: May 10, 1978

SUBJECT: PP NO. 7F1913, Additional comments supporting recommendations of review, 3/5/78.

FROM: Lawrence D. Chitlik
Toxicology Branch, RD (WH-567)

TO: Henry M. Jacoby, PM #24
Registration Division (WH-567)

THRU: Acting Chief
Toxicology Branch, RD (WH-567)

THRU: Pesticide Science Officer
Registration Division (WH-567)

Petitioner: Ciba-Geigy Corporation

Proposed Tolerance: 0.1 ppm of Metolachlor and its metabolites in or on soybeans and 0.02 ppm in eggs, milk, and the meat, fat of cattle, goats, hogs, horses, poultry and sheep.

TOX Branch notes the CHM review of D. Reed, 6/14/77, Conclusion #5, (Referenced also on pg. 3 of TOX review, 3/5/78) which states:

> "Establishment of the previous permanent tolerance on corn grain was based upon the likelihood of there being no human or animal exposure to residues of metolachlor. This use on soybeans would be expected to result in some human exposure to small residues of metolachlor."

TOX Branch was aware that only a small human exposure would have been expected from this proposed new use. On the other hand, we also noted deficiencies in the 90-Day rat and dog feeding studies (especially questions pertaining to histopathology) making these studies insufficient for a human health hazard assessment. As a result of these determinations we were unable to apply this data to a human health hazard equation (no matter how small the residues were to have been) and hence our unfavorable recommendations. Furthermore, the carcinogenicity evaluation is an IBT study audited by Ciba-Geigy personnel and numerous deficiencies have been noted in both the study report and the company audit and a revised report reflecting accurate results has been requested.

LC/cm

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EPA FORM 1320-6 (REV. 3-76)

**The exact fisher test for comparison of the basic probability of two binominal distributions; L. Sachs, Statistiche Auwertungsmethoden, Thime Verlag, Stutgart, 1971.

C. Discussion: No discussion necessary.

D. Conclusion: Technical metolachlor is a skin sensitizer in albino guinea pigs.

This study meets the requirements for skin sensitization.