

DATA EVALUATION RECORD

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 (Unpublished report prepared by the Oncins Research and Breeding Center for CIBA-GEIGY Corp., Greensboro, N.C.: CDL:94219-A).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 Uncins 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:

	<u>No. of Animals</u>				<u>Dose Level</u>
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.