



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

001051

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

DATE: October 5, 1981

SUBJECT: Proposed tolerances for Metolachlor on Sunflowers (0.3 ppm), Sunflower Meal and Hulls (0.6 ppm), PP#OF2416; Seed and Pod Vegetables (0.3 ppm), PP#1F2495; Sweet Corn and Popcorn (0.1 ppm), PP#1F2521; Cottonseed (0.1 ppm), 1F2506; Flaxseed (0.2 ppm), Flax straw (0.6 ppm), Flaxseed meal (0.4 ppm) and Flax hulls (0.4 ppm), OF2417 and 1H5293, Tox. Chem. No. 188DD, Acc. Nos. 244166, 099628, 099626, 070048

FROM: Gary J. Burin, Toxicologist
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Gary J. Burin 10/5/81

TO: Richard Mountfort (23)
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THRU: William Burnam, Acting Chief
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WLB
10-5-81

Requested Actions: Establishment of a permanent tolerances for residues of Metolachlor on sunflowers (0.3 ppm), sunflower meal and hulls (0.6 ppm), seed and pod vegetables (0.3 ppm), sweet corn and popcorn (0.1 ppm), cottonseed (0.1 ppm), flaxseed (0.2 ppm), flax straw (0.6 ppm), flaxseed meal (0.4) and flax hulls (0.4 ppm).

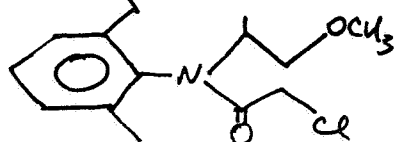
Recommendation:

Toxicology Branch is unable, at this time, to make a recommendation on the requested tolerances. Because the IBT Rat Chronic Feeding Study was positive in females at the high dose group, a risk assessment will be needed for the requested tolerances. This risk assessment is currently in progress. Toxicology Branch defers to RCB on the adequacy of existing meat and milk tolerances for the requested tolerances.

Common Names: Metolachlor, CGA-24705

Chemical Name: 2-chloro-N-(2-ethyl-6-methyl-phenyl)-N-(2-methoxy-1-methyl ethyl) acetamide

Chemical Structure:



Formulation: Dual 8E

Background Information

Toxicology Branch noted the need for long-term feeding studies, including an oncogenic evaluation, upon review of the first request by Ciba-Geigy for permanent tolerances of Metolachlor on May 27, 1975. An 18 month mouse oncogenicity study and a 2 year rat chronic feeding/oncogenicity study were received on 2/15/78 and on 1/18/78, respectively. Both of these studies were conducted at Industrial Biotest Laboratories and thus required validation prior to use in meeting regulatory requirements (For a summary of these and other studies submitted pursuant to the registration and petition for tolerances of Metolachlor, see the memo of February 7, 1980 from L. Chitlik. Also, see Toxicology Data Summary section of this memo for a listing of these studies). On December 17, 1979, L. Anderson of Toxicology Branch determined that the aforementioned chronic rat study was "Invalid" as a chronic feeding and "Supplementary" for oncogenic evaluation. Ciba-Geigy then contracted with the consulting firm of Drill, Friess, Hays, Loomis and Shaffer, Inc. to conduct a retrospective audit of the study. Their findings were discussed in the meeting of January 27, 1981 between EPA and Ciba-Geigy. As a result of that meeting, Toxicology Branch agreed to upgrade the study to Supplementary Data as an oncogenicity and as a chronic feeding study (See memo of July 28, 1981 from G. Burin and L. Chitlik). Due to the upgrading of this study to supplementary, an evaluation of the data was then necessary and a review is included in this action. The IBT mouse study has been classified as valid (See memo of December 13, 1979 from H. Spencer).

Toxicology Data Summary

<u>Study</u>	<u>Validity and/or Core Classification</u>	<u>Results</u>
2-year rat chronic study with oncogenicity evaluation (IBT)	Supplementary, Supplementary	Increased in primary liver tumors in males
2-year mouse oncogenicity evaluation (IBT)	Valid, Core-Minimum	Not oncogenic at 30, 1000 or 3000 ppm
Six month dog feeding study	Core-Minimum	NOEL = 100 ppm
90-day rat feeding study	Supplementary Data	

90-day dog feeding study	Core-Minimum	NOEL = 500 ppm
Teratology, rat	Core-Minimum	Not fetotoxic or teratogenic at the high dose, 360 mg/kg
3-generation reproduction study, rats (IBT)	Supplementary Data	No effects suggested up to 1000 ppm
Mouse dominant lethal study		Negative
Ames Mutagenicity Assay		Negative
(Summary primarily derived from Registration Standard. See Registration Standard for results of acute testing).		

Discussion:

Published Tolerances are as follows:

Corn, grain	0.1 ppm
Soybeans	0.1 ppm
Meat, inc. poultry	0.02 ppm
Milk and Dairy Products	0.02 ppm
Eggs	0.02 ppm

Tolerances Reviewed by Toxicology Branch but not yet published are as follows:

Sorghum grain	0.3 ppm
Sorghum forage and fodder	2.0 ppm
Peanuts	0.1 ppm
Peanut hulls	1.0 ppm
Peanut forage and hay	3.0 ppm

Tolerance held in abeyance by request of registrant:

Potatoes	0.1 ppm
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The corn, soybean, meat, milk and egg tolerances were established conditionally based upon the following requirements:

1. Re-evaluation of histopathology from the 90-day dog study would be submitted by 3/15/79.
2. The two-year rat study was to be submitted by 3/15/79.
3. No additional tolerances would be considered until the aforementioned studies were reviewed and accepted.
4. Ciba-Geigy will repeat their IBT mouse oncogenic study, although it is classified as Valid.

5. Ciba-Geigy agreed to initiate a 6 month dog study.

The aforementioned studies have all either been initiated or submitted. A repeat of the rat chronic/oncogenicity study is also underway. The only other additional data lacking, but desirable, is a 3-generation reproduction study to replace the IBT study classified as Supplementary Data. Per the Registration Standard for Metolachlor (September, 1980), a teratology study in a second species, was conducted and submitted (See Review, below).

The Allowable Daily Intake (ADI) is calculated as .0013 mg/kg/day in the Registration Standard, based on a NOEL of 100 ppm (2.5 mg/kg/day) in a six month dog study and a 2000 fold safety factor. It is noted that the safety factor which is currently used by Toxicology Branch for tolerances based on six month dog studies is 1000 fold rather than 2000 fold. Thus it is recommended, that the ADI for Metolachlor be changed to .0026 mg/kg/day based on a 1000 fold rather than a 2000 fold safety factor.

The Theroetical Maximum Residue Contribution (TMRC) from existing tolerances is 0.01712 mg/day/1.5 kg diet, including sorghum and peanuts, per the Registration Standard. The requested tolerances will contribute .019185 mg/day/1.5 kg diet additional residue.

A new TMRC, taking into account existing and requested tolerances, would thus be .036305 mg/day/1.5 kg of diet. This utilizes approximately 23.27% of the revised ADI.

Review of Data

1. Teratogenic Potential of CGA-24705 in New Zealand White Rabbits, performed at Argus Research Laboratories, Inc., Perkasi, Pa., July 25, 1980 and submitted by Ciba-Geigy Agricultural Division.

Sixty-four female New Zealand White rabbits were artificially inseminated with sperm from untreated, proven males from the same source and strain. Females were pretreated with Human Chorionic Gonadotropin prior to insemination.

Females were then randomly assigned to test groups which received either 0, 36, 120 or 360 mg/kg of CGA-24705 (95.4% pure) suspended in water with hydroxy methyl cellulose K 4M Premium (METHOCEL™) as the suspending agent. Animals received a volume of 10 ml/kg/day by gavage on days 6 through 18 of gestation based on body weight measurements which were made daily during the exposure period. Observations of clinical signs, abortions and delivery were made up to day 30 of gestation, at which time the does were killed by CO₂ asphyxiation and their uteri removed and examined. Fetuses and pups were then weighed and examined for visceral anomalies. Grossly observable visceral variations were removed, preserved with formalin and processed histologically. Finally, carcasses were eviscerated, stained with alizarin red S and examined for skeletal variations.

Results:

Maternal toxicity was evident in the high dose group in the form of lacrimation, miosis, decreased food consumption and decreased day 12 and 18 body weights. Of these signs of toxicity, only miosis was consistently found in the mid dose animals (one mid dose animal was reported to also have excess lacrimation). Thus, 360 mg/kg is the dose level in this study associated with frank maternal toxicity.

Two mortalities occurred in this study with one being found in the high dose group and one in the low dose group. Neither of the deaths were directly associated with the test compound although the intubation procedure and associated handling was likely to have been a precipitating factor in these deaths.

No compound-related effects were observed on litter size, numbers of early or late resorptions, fetal body weights, or frequency of variations among fetuses or pups. Among the specific variations observed, no compound related effects were evident. Although hydrocephalus with small exencephaly was observed in two fetuses from a dam treated with 360 mg/kg and was not seen in control, low or mid dose fetuses, the low incidence of this variation and the maternal toxicity seen in the dam which delivered those pups, suggest that it was not a true teratogenic response and that it may be either spontaneous in origin or associated with the maternal toxicity.

Core Classification

Core-Minimum. The NOELs for teratogenicity and fetal toxicity are 360 mg/kg. Frank maternal toxicity was observed only at the 360 mg/kg dose level.

2. Six Month Interim Report of a Two-Year Oral Feeding Study of Metolachlor in Rats, conducted at Raltech Scientific Services and submitted by Ciba-Geigy on January 28, 1981.

Albino CD rats are being fed either 0, 30, 300 or 3000 ppm in the diet. Seventy rats per group were started on test and at least 60 rats remain in each test group. Mean body weight of high dose males was slightly less than that of controls, low or mid dose males (586 vs. 597, 614, and 624, respectively) at Week 26. Mean body weight of high dose females was significantly less than that of controls, low or mid dose females (319 vs. 343, 344 and 346). No other compound related effects were observed with two possible exceptions - SGOT appears to be decreased in a dose-related fashion in both males and females and SGPT appears to be decreased in both high dose males and females.

It is noted that SGOT was also significantly decreased ($p < .05$) in 3000 ppm males at the 6-month measurement in the previous Two-Year Oral Feeding Study in Rats, conducted at IBT (discussed below).

3. Two-Year Chronic/Oncogenicity Oral Toxicity Study in Albino Rats, performed at Industrial Biotech Laboratories Study No. 622-07926, Decatur, Illinois, February 9, 1979 and submitted by Ciba-Geigy Agricultural Division.

(This study has been validated and is classified as Supplementary Data as both a chronic feeding study and as an oncogenicity study).

Sixty male and 60 female Charles River strain albino rats were fed diet containing 0, 30, 300, 1000 and 3000 ppm of CGA-24705 Technical. Feeding was initiated when animals were 29 days of age. Animals were housed individually in wire-bottomed steel cages and diet was prepared by the blending of test compound in a high speed blender. Batch#FL-750227 (99.9% purity) was used during week 1-29 and Batch#FL-752105 was used for all following weeks. Diet preparation records support weekly diet preparation with the exceptions of periods between January 2 and March 3, 1976 (8 weeks) and between May 4 and July 15, 1976 (9 weeks). Diet samples were collected at months 0, 3, 6, 12, 15, 17, 18 and 20 and weekly for the remainder of the study. Food consumption data were collected from 20 rats per sex week for 13 weeks and monthly thereafter.

Each animal was weighed weekly for 13 weeks and monthly thereafter. Observations were recorded sporadically. Blood and urine samples were taken after 3, 6, 12, 18 and 24 months of testing from 20 rats per sex of the control and high dose groups. Ten additional animals per sex were on test in the control and high dose groups to month 12, at which time the animals were removed from test and either immediately sacrificed (5 animals per sex per group) or allowed a one month recovery period prior to sacrifice. Blood was analyzed for total leukocyte count, erythrocyte count, hemoglobin concentration, hematocrit, differential leukocyte count, platelet count, MCV, MCH, MCUC, SAP, SGPT, SGOT, BUN, Glucose, total cholesterol and total protein. Urine was analyzed for glucose, albumin, pH, specific gravity, and microscopic elements.

Gross and microscopic examinations were performed on all animals unless precluded by autolysis. Tissues examined included:

Adrenals	Pancreas
Aorta (thoracic)	Parathyroid glands
Brain (cerebrum, cerebellum, pons)	Peripheral nerve (sciatic)
Caecum	Pituitary gland
Colon	Prostate gland
Epididymides	Salivary gland (submaxillary)
Esophagus	sublingual, parotid)
Eyes with optic nerves	Small intestine (duodenum, jejunum, ileum)
Femur	Spinal cord
Gonads	Spleen
Heart	Sterum (bone marrow)
Kidneys	Stomach (cardia, fundus, pylorus)
Liver	Thyroid glands
Lung	Trachea
Lymph nodes (cervical, mediastinal, mesenteric)	Urinary bladder
Mammary gland	Uterus
Muscle (skeletal)	

Results:

(Diet analysis records indicate that all test groups ingested diet containing somewhat less test compound than was intended. Time weighted average levels of CGA-24705 in the diet were 27.1, 254.5, 945.1 and 2457.1 ppm for the 30, 300, 1000 and 3000 ppm targeted levels (See memo of August 14, 1979 by L. Anderson). Although this per se does not effect the validity of the study or it's results, it should be taken into account in the association of given levels of test compound with toxicological effects.)

The mean body weight of high dose males was significantly ($p < .05$) less than controls from month 18 to study termination and sporadically less than controls prior to month 18. Female mean body weight of the high dose group was significantly less than controls from month 21 to study termination and sporadically less than controls prior to month 18. Group T-III female mean body weight were sporadically less than control females. Mean body weights of other test groups were similar to controls.

Food consumption of all male and female test groups were comparable to their corresponding controls.

Clinical chemistry, hematology and urinalysis of high dose males and females (the only test groups examined) were unremarkable with the exception of SGOT in males, which was significantly ($p < .05$) less than controls at the 3, 6 and 12 month measurements. This parameter was not significantly effected at the 18 and 24 month measurements.

The histopathology and organ weights of the 12 month sacrifice animals were unremarkable compared with control animals.

Among the T-IV animals removed from test at month 12 and allowed a 4 week recovery period, only the thyroid to body weight ratios were remarkable. The thyroid to body weight ratio was significantly less ($p < .01$) in females and slightly less in males. Absolute thyroid weight was not effected by treatment, suggesting that the decreased thyroid to body weight ratios are likely the result of a decreased body weight in high dose animals.

Among final sacrifice animals, the brain to body weight ratios of both males and females were significantly increased ($p < .05$). Absolute spleens weight were significantly less than controls in T-II, T-III and T-IV males. T-III female spleen was significantly less than control and T-IV female spleen weight was slightly less than controls. Liver weight comparisons were unremarkable.

No treatment related gross lesions were evident. Histopathologic lesions suggestive of treatment-related effects were found only in the liver. Focal hepatocellular hypertrophy and hyperplasia incidences were similar in all groups. Curiously, extramedullary hematopoiesis incidences appeared to be decreased among treated animals. Incidences were 16, 4, 12, 6 and 5 of 0, 30, 300, 1000 and 3000 ppm males and 20, 15, 14, 18 and 5 of the 0, 30, 300, 1000 and 3000 ppm males were diagnosed as having focal extramedullary hematopoiesis of the liver.

One or more "Hypertrophic-hyperplastic nodules" were found in the liver of 2/55, 2/58, 0/55, 4/51 and 5/54 males of 0, 30, 300, 1000 and 3000 ppm dose groups, respectively.

Among females, the incidence was 1/54, 1/59, 3/60, 3/60 and 9/60 in the 0, 30, 300, 1000 and 3000 ppm groups.

Among other neoplastic lesions, only two types were remarkable and both of these were found in the liver of females. Cystic cholangioma was found in the liver of 2/54, 2/58, 1/60, 2/60 and 6/60 of the 0, 30, 300, 1000 and 3000 ppm groups respectively. Hepatocellular carcinoma, a relatively rare tumor in females of this strain of rat, was found in two high dose females and not in any other group of females. Histopathologic diagnoses of male and female liver lesions are summarized in the following tables:

Table 1
Primary Liver Tumors in Females

	PPM				
	0	30	300	1000	3000
Hypertrophic-Hyperplastic nodule	0	1	2	1	3
Hypertrophic-Hyperplastic nodules	1	0	1	2	6
Angiosarcoma	0	0	0	0	1
Cholangioma	0	0	1	0	0
Cystic cholangioma	2	2	1	2	6
Hepatocellular carcinoma	0	0	0	0	2
Total (# animals with primary liver tumors)	3	3	5	5	15*
Number examined (month 13-Final sacrifice)	54	58	60	60	60

*Three animals each bore two primary liver tumors.

Table 2
Primary Liver Lesions in Males

	PPM				
	<u>0</u>	<u>30</u>	<u>300</u>	<u>1000</u>	<u>3000</u>
Hypertrophic-Hyperplastic nodule	1	0	2	2	1
Hypertrophic-Hyperplastic nodules	0	0	0	0	1
Angiosarcoma	0	0	1	0	0
Hepatocellular carcinoma	2	1	1	1	3
Total (# animals with primary liver tumors)	3	1	4	3	5
Number examined (month 13-Final sacrifice)	55	55	54	50	54

Thus an increase in the incidence of primary liver tumors is found only in high dose females. The probability that this increase is due to chance is small ($P < .005$) and the variety of forms of tumor expression in the liver suggest that though the liver is a target organ, a variety of cell types and locations may be effected within the liver.

Core-Classification: Supplementary Data. A NOEL was not established. Validation deficiencies are presented in the memos of December 17, 1979 and August 14, 1979 from L. Anderson.