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

FEB 8 1982

MEMORANDUM

OFFICE OF  
PESTICIDES AND TOXIC SUBSTANCES

DATE: ~~February 4, 1982~~

SUBJECT: Proposed Tolerance for Metolachlor on Safflower Seed  
(0.1 ppm), PP#2F2601      Tox. Chem.#188DD

FROM: Gary J. Burin, Toxicologist  
Toxicology Branch/HED (TS-769)

*Gary J Burin* *JDC*  
*2/4/82*

TO: Richard Mountfort (23)  
Registration Division (TS-767)

THRU: Orville E. Paynter, Chief  
Toxicology Branch/HED (TS-769)

*def OSP*

Registrant: Ciba-Geigy Corp.  
Agricultural Division  
P.O. Box 11422  
Greensboro, N.C. 27409

Requested Action: Establishment of a permanent tolerance  
for residues of Metolachlor on safflower seed (0.1 ppm).

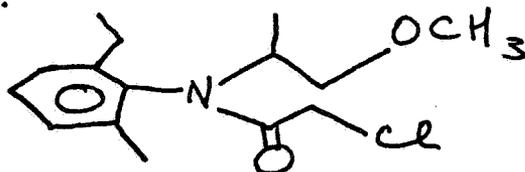
Background Information: Metolachlor has been shown to be associated with an increased incidence of primary liver tumors in female rats at a dose level of 3000 ppm ( $p < .005$ , see my review of October 7, 1981). A risk assessment has been performed based on this finding and was presented in my review of January 29, 1982.

Recommendation: Aside from oncogenic risk, Toxicology Branch does not object to the requested tolerance and defers to RCB on the adequacy of existing meat and milk tolerances for the requested new use. The increase in oncogenic risk resulting from the requested use is estimated to be  $1.14 \times 10^{-9}$ . Toxicology Branch defers to the Administrator regarding the acceptability of this risk (See Discussion). The % of ADI utilized will increase approximately .086 as a result of this tolerance.

Common Name: 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

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	Increase 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
Two-generation reproduction study, rats	Core-Guidelines	NOEL = 300 ppm
Teratology, rabbits	Core-Minimum	NOEL = 360 mg/kg for maternal and fetotoxicity
One-Year Interim Report, Two-Year Oral, rats	Supplementary Data	NOEL = 300 ppm

(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	0.2 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
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 ppm
Flax hulls	0.4 ppm
Potatoes	0.2 ppm

The Allowable Daily Intake (ADI) is calculated as .0026 mg/kg/day, based on a NOEL of 100 ppm (2.5 mg/kg/day) in the six month dog study and a 1000 fold safety factor. The TMRC, taking into account existing and Toxicology Branch reviewed tolerances, is .052505 mg/kg/1.5 kg of diet. This utilizes approximately 33.66% of the ADI. The requested tolerance will contribute .045 ng/kg/1.5 kg and will utilize an additional .086% of the ADI. The new TMRC would thus be .05255 mg/kg/1.5 kg and would utilize 33.75% of the ADI.

A risk assessment based on the chronic rat feeding study conducted at IBT indicates that the point estimate of oncogenic risk resulting from dietary exposure to existing and Toxicology Branch - reviewed tolerances is  $2.167 \times 10^{-7}$  and the upper 95% bound on this increased risk estimate is  $8.0 \times 10^{-7}$  (see my memo of January 28, 1982). Given the  $Q_1^*$  estimate of  $2.04 \times 10^{-3}$ , the point estimate of additional risk from this new use will be  $1.14 \times 10^{-9}$ .

ACCEPTABLE DAILY INTAKE DATA

DOJ	DEL	S.F.	ADI	MPI
mg/kg	ppm		mg/kg/day	g/day(60kg)
2.500	100.00	1000	0.0025	0.1500

Published Tolerances

CROP	Tolerance	Food Factor	mg/day(1.5kg)
Corn, grain( 88)	0.100	1.00	0.00150
Soybeans (oil)(148)	0.100	0.92	0.00138
Meat, inc poultry( 89)	0.020	13.85	0.00415
Milk&Dairy Products( 93)	0.020	25.62	0.00858
Eggs( 54)	0.020	2.77	0.00083
Peanuts(115)	0.100	0.36	0.00054
Sorghum(147)	0.300	0.03	0.00014

MPI	TIIRC	% ADI
0.1500 mg/day(60kg)	0.0171 mg/day(1.5kg)	11.41

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Unpublished, Tox Approved SF2203, 2416, 2495, 2506, 2521

CROP	Tolerance	Food Factor	mg/day(1.5kg)
Potatoes(127)	0.200	5.43	0.01628
Sunflower(150)	0.300	0.03	0.00014
Seed&pod veg(143)	0.300	3.66	0.01646
Corn, pop( 39)	0.100	0.08	0.00012
Corn, sweet( 40)	0.100	1.43	0.00215
Cottonseed (oil)( 41)	0.100	0.15	0.00022

MPI	TIIRC	% ADI
0.1500 mg/day(60kg)	0.0525 mg/day(1.5kg)	34.99

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