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

JUL 21 1993

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Carcinogenicity Peer Review of Metolachlor (3rd)

FROM: Stephen C. Dapson, Ph.D. Stephen C. Dapson 6/29/93
Toxicologist, Review Section I
Toxicology Branch II
Health Effects Division (H7509C)

and

Esther Rinde, Ph.D. Esther Rinde
Manager, Carcinogenicity Peer Review Committee
Science Analysis and Coordination Branch
Health Effects Division (H7509C)

TO: Joanne Miller
Product Manager #23
Herbicide-Fungicide Branch
Registration Division (H7505C)

and

Walter Waldrop
Section Head
Accelerated Reregistration Branch
Special Review and Reregistration Division (H7505W)

THROUGH: Penelope Fenner-Crisp, Ph.D. Penelope A. Fenner-Crisp
Director, Health Effects Division (H7509C)

The Health Effects Division Carcinogenicity Peer Review Committee (PRC) met on May 30, 1985 (first meeting), April 17, 1991 (second meeting) and on April 14, 1993 (present meeting) to discuss and evaluate the weight-of-the-evidence on Metolachlor with particular reference to its carcinogenic potential.

The Peer Review Committee agreed that Metolachlor should be classified as Group C - possible human carcinogen and recommended that for the purpose of risk characterization a low dose extrapolation model applied to the experimental animal tumor data should be used for quantification of human risk (q_1*).

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A. Individuals in Attendance:

1. Peer Review Committee: (Signatures indicate concurrence with the peer review unless otherwise stated.)

Penny Fenner-Crisp	Penelope A. Fenner-Crisp
Reto Engler	
William L. Burnam	
Karl Baetcke	
Marion Copley	
Kerry Dearfield	
Julie Du	
Hugh Pettigrew	
Esther Rinde	

2. Reviewers: (Non-committee members responsible for data presentation; signatures indicate technical accuracy of panel report.)

Stephen C. Dapson[1]	
Mike Ioannou	
Lori Brunsman	
Lucas Brennecke[2] (PAI/Clement)	

3. Other Attendees:

Linda Kutney, Jim Rowe (HED)

Diane Mandell (Clement)

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[1]Also a member of the PRC for this chemical; signature indicates concurrence with the peer review unless otherwise stated.

[2]Signature indicates concurrence with pathology report.

B. Material Reviewed:

The material available for review consisted of DER's, one-liners, and other data summaries prepared by Dr. Stephen Dapson, pathology report analysis by L. Brennecke, the FIFRA Scientific Advisory Panel (SAP) meeting notes on Metolachlor, new data provided by the registrant, and tables and statistical analysis by Lori Brunsman. The material reviewed is attached to the file copy of this report. The data reviewed are based on studies submitted to the Agency by Ciba-Geigy Corporation.

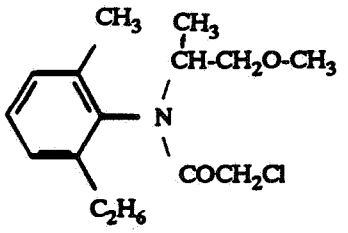
C. Background Information:

Metolachlor is the common name for 2-chloro-N-(2-ethyl-6-methylphenyl)-N-(2-methoxy-1-methylethyl) acetamide, one of the family of chloroacetanilides.

Metolachlor is a selective herbicide registered for use (CFR 180.368) for the control of most annual grasses and certain broadleaf weeds in corn, soybeans, peanuts, grain sorghum, potatoes, pod crops, cotton, safflower, and woody ornamentals.

The Caswell (or Tox Chem) Number of Metolachlor is 188DD.
The Chemical Abstracts Registry Number (CAS No.) is 51218-45-2.

The structure of Metolachlor is shown below:



The PRC first met on May 30, 1985 to review the evidence for the carcinogenic classification of Metolachlor. The Committee concluded that "the data available for Metolachlor provide weak evidence of carcinogenicity," but did not assign a carcinogenicity classification. Their evaluation was based on a chronic Industrial Biotest Laboratories (IBT) rat study (IBT rat study No. 622-07925), and a second chronic (2-year) rat study performed by Hazleton-Raltech Inc. (No. 80030); a 2-year chronic mouse study performed by IBT (No. 622-07925), and a second 2-year chronic mouse study by Hazleton-Raltech Inc.; two genotoxicity assays (mouse dominant lethal study, Salmonella mutagenicity assay); and four developmental studies using Metolachlor. Before making a final evaluation regarding the classification and calculation of a potency factor (q_1^*) for Metolachlor, the PRC requested additional information from the registrant to fulfill

the mutagenicity battery and metabolism study requirements, based on 1982 EPA testing guidelines.

The second peer review meeting on Metolachlor took place on April 17, 1991. The PRC recommended that Metolachlor be classified as Group C, and that quantification of risk be performed using a linearized multistage model (q_1^*). This recommendation was based on the replication of hepatic neoplasia in female rats in the first (IBT) and second (Hazleton-Raltech) rat carcinogenicity studies, and the apparent induction of a small number of nasal turbinate tumors (an uncommon tumor induced by certain analogs of Metolachlor) at the highest dose tested (HDT) in the second rat study. The material reviewed included the database from the first PRC meeting and supplemental pathology reports and historical control data submitted by the registrant in 1988. Additional data on metabolism and genotoxicity were also reviewed. The PRC recommended the completion of an <u>in vivo</u>/<u>in vitro</u> unscheduled DNA synthesis assay.

A q_1^* was calculated for Metolachlor of 2.1×10^{-3} $(mg/kg/day)^{-1}$ (q_1^* from Memorandum dated January 29, 1982, G.J. Burin to R. Mountfort). Exposure assessment was conducted by the Occupational and Residential Exposure Branch (Memorandum dated May 10, 1990, C. Lunchick to R. Ikeda) and an average daily exposure of 1.1×10^{-4} mg/kg/day was calculated. The estimated risk is 2.3×10^{-7}.

The SAP met on September 18, 1991 to review the classification of Metolachlor. The SAP considered the evidence to be "minimal but sufficient for the classification of Metolachlor as a Group C carcinogen." According to the registrant, the information provided to the SAP in a briefing paper was supplemental to the data submitted in 1988, and served to clarify and correct several data points in the 1988 submission (Dr. William Field's reading of control male adenocarcinoma and male 300 ppm adenomous polyp is stated to be overestimated). The registrant further claimed that "application of quantitative risk assessment to a marginal Class C oncogen like Metolachlor in order to facilitate comparison of cancer potency of Metolachlor with other members of this class of herbicides as stated in EPA's second Peer Review, is scientifically unfounded."

The third peer review meeting (present meeting, April 14, 1993) was held to consider the additional data submitted by Ciba-Geigy pertaining to Metolachlor's carcinogenicity potential (even though the information had previously been submitted to the PRC as part of the April 17, 1991 peer review package), since the registrant felt that the data were not adequately considered by the committee; specifically, the submitter requested a formal review of the document submitted in 1988, and a review of the company's document entitled "Metolachlor, Briefing Paper for the Scientific Advisory Panel" submitted to the SAP in September

1991. The registrant originally stated that Metolachlor is not carcinogenic; however, in the SAP briefing paper they call it a "weak C" carcinogen.

D. Evaluation of Carcinogenicity Evidence:

1. Charles River CD Rat Chronic Feeding Carcinogenicity Study

Reference: Chronic toxicity/carcinogenicity study in Charles River Crl:CD(SD)BR albino rats. MRID No. 129377-00. Study No. 80030. Hazleton Raltech Incorporated, Madison, WI; for Ciba-Geigy Corporation, Greensboro, NC. Submitted May 2, 1983.

a. Experimental Design

Metolachlor was administered in the diet to 70 animals per sex at doses of 0 or 3000 ppm, and to 60 animals per sex at doses of 30 or 300 ppm. Ten animals per sex in the control and 3000 ppm dose groups were designated for interim sacrifice, five at week 53 and five at week 57 following a 4-week recovery period.

b. Discussion of Tumor Data

Initially, all slides were read by Hazleton Raltech, Incorporated. Ciba-Geigy Corporation subsequently requested Dr. Jerry F. Hardisty of Experimental Pathology Laboratories, Incorporated, (EPL) to re-read only the liver slides (issued on July 20, 1984). EPL then conducted their own internal peer review of Dr. Hardisty's read of the slides by presenting only those slides of animals on which Dr. Hardisty found liver lesions and an additional six female control blanks to a panel of six pathologists, including Dr. Hardisty. For this reason, statistical analysis was not conducted. In addition, Ciba-Geigy requested Dr. Kevin T. Morgan, under contract to EPL, to re-read only the nasal passages slides [issued May 4, 1988 (Attachments 2 and 4 of MRID No. 409344-01 from Ciba-Geigy dated November 18, 1988)]. A memorandum from Dr. Lucas H. Brennecke to Dr. Stephen Dapson dated July 20, 1992 was also considered by the PRC.

Statistical analysis of tumor rates was based on the Exact Trend Test and Fisher's Exact Test for the pair-wise comparison of controls and each treated group, since there were small occurrences of tumors and no significant statistical evidence of mortality with increasing doses of Metolachlor.

Significant increasing trends in liver adenomas ($p < 0.01$, Hazleton; $p < 0.05$, Hardisty) and combined liver adenomas and/or carcinomas ($p < 0.05$ for both reports) were observed in male rats (Tables 1 and 2). There were no significant differences in the pair-wise comparisons of the controls with the dosed groups.

Table 1. Metolachlor - Charles River Crl:CD(SD)BR Rat Study

Male Liver Tumor Rates[+] and Exact Trend Test
and Fisher's Exact Test Results (p values)

Pathology Report By:
Hazleton Raltech, Incorporated
May 2, 1983

	Dose (ppm)			
Tumors:	0	30	300	3000
Neoplastic Nodules (Adenomas)	0/58	0/57	0/59	4[a]/60
(%)	(0)	(0)	(0)	(7)
p =	0.004**	1.000	1.000	0.064
Hepatocellular Carcinomas	2[b]/58	1/57	3/59	2/60
(%)	(3)	(2)	(5)	(3)
p =	0.432	0.507[n]	0.508	0.678
Combined	2/58	1/57	3/59	6/60
(%)	(3)	(2)	(5)	(10)
p =	0.027*	0.507[n]	0.508	0.147

[+]Number of tumor bearing animals/Number of animals examined, excluding those that died or were sacrificed before week 53.

[n]Negative change from control.

[a]First neoplastic nodule observed at week 82, dose 3000 ppm.

[b]First hepatocellular carcinoma observed at week 74, dose 0 ppm.

Note: Significance of trend denoted at control.

Significance of pair-wise comparison with control denoted at dose level.

If *, then $p < 0.05$. If **, then $p < 0.01$.

Table 2. Metolachlor - Charles River Crl:CD(SD)BR Rat Study

Male Liver Tumor Rates[+] and Exact Trend Test
and Fisher's Exact Test Results (p values)

Pathology Report By:
Dr. Jerry F. Hardisty
July 20, 1984

	Dose (ppm)			
Tumors:	0	30	300	3000
Hepatocellular Adenomas	1/58	1/57	0/59	4/60
(%)	(2)	(2)	(0)	(7)
p =	0.035*	0.748	0.496[n]	0.193
Hepatocellular Carcinomas	2/58	1/57	3/59	3/60
(%)	(3)	(2)	(5)	(5)
p =	0.247	0.507[n]	0.508	0.516
Combined	3/58	2/57	3/59	7/60
(%)	(5)	(4)	(5)	(12)
p =	0.037*	0.508[n]	0.652	0.175

[+]Number of tumor bearing animals/Number of animals examined, excluding those that died or were sacrificed before week 53.

[n]Negative change from control.

Note: Significance of trend denoted at control.

Significance of pair-wise comparison with control denoted at dose level.

If *, then $p < 0.05$. If **, then $p < 0.01$.

In female rats, an increased trend is indicated in liver adenomas and combined liver adenomas and/or carcinomas ($p < 0.01$ for both parameters in both reports) (Tables 3 and 4). Significant pair-wise comparisons were found in the 3000 ppm dose group for liver adenomas ($p < 0.05$) based on the Hardisty report, and for combined liver adenomas and/or carcinomas ($p < 0.05$, Hazleton; $p < 0.01$, Hardisty).

Dr. Hardisty's concluded that, "the increased incidence of hepatocellular neoplasms observed in female rats given 3000 ppm is considered to be equivocal due to their low incidence and similarity to published incidences for aged rats of this strain." The PRC disagreed with this conclusion. Furthermore, according to

a memorandum from Dr. Lucas H. Brennecke to Dr. Stephen Dapson, July 20, 1992,

> "The 1988 re-evaluation of liver slides for all female rats by a panel of five pathologists revealed that the incidences of adenomas and adenomas/carcinomas (combined) were significantly ($p \leq 0.05$) greater than controls. In only one of the 12 studies showing historical control incidence of liver tumors in Sprague-Dawley rats at Hazleton did the incidence of adenomas or combined adenomas and carcinomas exceed that noted in the Metolachlor study. In that study (#12), the historical incidence of liver tumors was clearly higher (more than twice) than in any other study. As such, it should not be given much weight in considering the real historical incidence at Hazleton."

Table 3. Metolachlor - Charles River Crl:CD(SD)BR Rat Study

Female Liver Tumor Rates[+] and Exact Trend Test
and Fisher's Exact Test Results (p values)

Pathology Report By:
Hazleton Raltech, Incorporated
May 2, 1983

	Dose (ppm)			
Tumors:	0	30	300	3000
Neoplastic Nodules (Adenomas) (%)	0/58 (0)	0/60 (0)	1[a]/58 (2)	4/57 (7)
p =	0.005**	1.000	0.500	0.057
Hepatocellular Carcinomas (%)	0/58 (0)	0/60 (0)	0/58 (0)	2[b]/57 (4)
p =	0.059	1.000	1.000	0.244
Combined (%)	0/58 (0)	0/60 (0)	1/58 (2)	6/57 (11)
p =	0.000**	1.000	0.500	0.013*

[+]Number of tumor bearing animals/Number of animals examined, excluding those that died or were sacrificed before week 53.

[a]First neoplastic nodule observed at week 104, dose 300 ppm.

[b]First hepatocellular carcinoma observed at week 90, dose 3000 ppm.

Note: Significance of trend denoted at control.

Significance of pair-wise comparison with control denoted at dose level.

If *, then $p < 0.05$. If **, then $p < 0.01$.

Table 4. Metolachlor - Charles River Crl:CD(SD)BR Rat Study

Female Liver Tumor Rates[+] and Exact Trend Test
and Fisher's Exact Test Results (p values)

Pathology Report By:
Dr. Jerry F. Hardisty
July 20, 1984

	Dose (ppm)			
Tumors:	0	30	300	3000
Hepatocellular Adenomas	0/58	1/60	2/58	6/57
(%)	(0)	(2)	(3)	(11)
p =	0.002**	0.509	0.248	0.013*
Hepatocellular Carcinomas	0/58	0/60	0/58	1/57
(%)	(0)	(0)	(0)	(2)
p =	0.245	1.000	1.000	0.496
Combined	0/58	1/60	2/58	7/57
(%)	(0)	(2)	(3)	(12)
p =	0.001**	0.509	0.248	0.006**

[+]Number of tumor bearing animals/Number of animals examined; no tumors were found in animals that died or were sacrificed before week 53.

Note: Significance of trend denoted at control.

Significance of pair-wise comparison with control denoted at dose level.

If *, then $p < 0.05$. If **, then $p < 0.01$.

Historical control data for the incidence of hepatocellular tumors in female rats for contemporary studies conducted at Hazleton Laboratories in Madison, Wisconsin, five years prior to and after the Metolachlor study are shown below:

Hepatocellular lesion type	Historical control range[a] Mean (%)	Range (%)
Adenoma	2.1	0-11.5[b]
Carcinoma	0.2	0- 1.9
Combined	2.3	0-13.5[c]

[a]Based on 12 studies conducted at Hazleton Laboratories in Madison, Wisconsin between the years 1980 and 1984.
[b]The distribution of adenoma (percent incidence) from the 12 individual studies was as follows: 0, 0, 3.3, 0, 0, 4.0, 5.1, 0, 0, 1.4, 1.7, 11.5.
[c]The distribution of combined adenoma/carcinoma (percent incidence) from the 12 individual studies was as follows: 0, 0, 3.3, 0, 0, 4.0, 5.1, 0, 0, 1.4, 1.7, 13.5.

No statistical analysis was performed on the nasal pathology report by Dr. Morgan of EPL because the tumor occurrences were too small to indicate statistical trends or pair-wise comparisons at any level of significance. The PRC agreed that it would be inappropriate to combine these lesions because the three neoplasms were not of the same type, nor did they originate in similar tissue (Memorandum from Dr. Lucas H. Brennecke to Dr. Stephen Dapson, July 20, 1992). Therefore, the PRC agreed to accept the conclusion of Dr. Morgan that "there is no evidence of treatment-related nonneoplastic or neoplastic responses in the nasal passages of male or female Charles River CD Albino rats given 30, 300, or 3000 ppm Metolachlor in this study." In addition, the PRC discussed the possibility that there may be in situ formation of formaldehyde from Metolachlor; no data were available to support or contradict this possibility. Nasal tumor data from the Morgan report are presented in Tables 5 and 6 for males and females, respectively.

Table 5. Metolachlor - Charles River Crl:CD(SD)BR Rat Study
Male Nasal Tumor Rates+

Pathology Report By:
Dr. Kevin T. Morgan
May 4, 1988

	Dose (ppm)			
Tumors:	0	30	300	3000
Polypoid Adenomas (Respiratory Epithelium)	1/64	0/56	0/53	1/67
Adenocarcinomas (Nasal Glands)	0/64	0/56	0/53	1/67
Neurofibrosarcomas (Peripheral Nerve)	0/64	0/56	0/53	1/67
Malignant Lymphomas (Metastatic)	0/64	2/56	0/53	0/67

+Number of tumor bearing animals/Number of animals examined.

Table 6. Metolachlor - Charles River Crl:CD(SD)BR Rat Study
Female Nasal Tumor Rates+

Pathology Report By:
Dr. Kevin T. Morgan
May 4, 1988

	Dose (ppm)			
Tumors:	0	30	300	3000
Polypoid Adenomas (Respiratory Epithelium)	0/67	0/51	1/56	0/67
Odontomas	1/67	0/51	0/56	1/67
Squamous Papillomas	0/67	0/51	0/56	1/67

+Number of tumor bearing animals/Number of animals examined.

c. Non-neoplastic Lesions and Other Observations

The statistical evaluation of mortality indicated no significant incremental changes with increasing doses of Metolachlor in male or female rats (Tables 7 and 8).

Table 7. Metolachlor - Charles River Crl:CD(SD)BR Rat Study

Male Mortality Rates[+] and Cox or Generalized K/W Test Results

	Weeks					
Dose(ppm)	1-26	27-52	53[i]	53-78	79-105[f]	Total
0	1/70	1/69	10/68	9/58	16/49	27/60 (45)
30	0/60	3/60	0/57	5/57	18/52	26/60 (43)
300	1/60	0/59	0/59	3/59	31/56	35/60 (58)
3000	0/70	0/70	10/70	5/60	21/55	26/60 (43)

[+]Number of animals that died during interval/Number of animals alive at the beginning of the interval.

[i]Interim sacrifice at week 53.

[f]Final sacrifice at week 104.

( )Percent.

Note: Time intervals were selected for display purposes only.

Significance of trend denoted at control.

Significance of pair-wise comparison with control denoted at dose level.

If *, then $p < 0.05$. If **, then $p < 0.01$.

Table 8. Metolachlor - Charles River Crl:CD(SD)BR Rat Study

Female Mortality Rates[+] and Cox or Generalized K/W Test Results

	Weeks					
Dose(ppm)	1-26	27-52	53[i]	53-78	79-105[f]	Total
0	0/70	2/70	10/68	7/58	18/51	27/60 (45)
30	0/60	0/60	0/60	12/60	18/48	30/60 (50)
300	0/60	2/60	0/58	7/58	22/51	31/60 (52)
3000	2/70	1/68	10/67	3/57	14/54	20/60 (33)

[+]Number of animals that died during interval/Number of animals alive at the beginning of the interval.

[i]Interim sacrifice at week 53.

[f]Final sacrifice at week 104.

( )Percent.

Note: Time intervals were selected for display purposes only.

Significance of trend denoted at control.

Significance of pair-wise comparison with control denoted at dose level.

If *, then $p < 0.05$. If **, then $p < 0.01$.

Female rats had reversible weight loss from study weeks 2 to 104; food consumption was reduced in female rats during intermittent periods during the study. Male rats exhibited testicular atrophy with degeneration of tubular epithelium. The severity of the effect was reported to be similar in all treated groups but the time of onset was sooner in all treated males. Finally, there was an increased incidence of eosinophilic foci in the livers of both male (10/59 control, 15/59 low, 14/60 mid, 21/60 high) and female (4/60 control, 7/60 low, 5/60 mid, 23/60 high) rats upon histological examination.

d. Adequacy of Dosing for Assessment of Carcinogenic Potential

The dosing was considered to be marginally adequate for assessing the carcinogenic potential of Metolachlor, based on decreased body weight gain (13%) and decreased food consumption in 3000 ppm females, testicular atrophy and degeneration in treated

males, and liver histopathology in male and female rats. The PRC had difficulty establishing if the doses used in this study were high enough to establish without a doubt that the nasal tumors that were seen in rats dosed with 3000 ppm Metolachlor were indeed spurious.

2. Other carcinogenicity studies

Not considered by the PRC was a chronic feeding study in rats submitted by Industrial Biotest Laboratory (MRID No. 244166, 099628, 099626, 070048; study No. 622-07925, Submitted February 9, 1979). This study was classified as Core-Supplementary because of inadequate clinical chemistry determinations and dietary preparation records. Although not discussed in detail, the PRC noted that liver hyperplastic nodules and carcinomas occurred in female rats at the HDT (3000 ppm) in this study; these agreed with the results of the repeat Hazleton rat study. Further detail is provided in Section D.1 of the second peer review document.

See Sections D.3. and D.4. of the second peer review document for description of two negative mouse carcinogenicity studies (IBT's 2-year mouse study No. 622-07925; Hazleton-Raltech 2-year repeat mouse study No. 79020). These mouse studies were not discussed further by the PRC.

E. Additional Toxicology Data on Metolachlor:

1. Metabolism

Reference: Disposition of Metolachlor in the Rat (General Metabolism). MRID No. 401144-01. Study No ABR-8611. Ciba-Geigy Corporation. Submitted February 17, 1987.

A single low (1.5 mg/kg), a single high (300 mg/kg), and repeated low (1.5 mg/kg/day for 15 days) oral doses of Metolachlor were used. These doses were found to be readily absorbed and excreted by male and female rats. The urinary and fecal elimination of radioactivity was essentially complete within 48 to 72 hours postdosing. Approximately 48 to 64 % of the radiolabel was recovered within 7 days with similar amount in the feces. Low levels of radioactivity were found in the tissues of all animals at 7 days postdosing.

This study is classified as Core-Supplementary Data since the study did not provide the purity of the test compound used and the metabolites were not identified. This study alone does not satisfy the guideline requirement (§85-1) for a metabolism study in the rat, and only provides supplementary information on the metabolism of single low, single high, and repeated oral doses of Metolachlor.

Reference: Kinetics of Metolachlor, a report by I.W.F. Davidson, October 14, 1988. In this report, a kinetics modelling system was applied to data from the following DER:
Disposition of Metolachlor in the Rat (General Metabolism). MRID No. 401144-01. Study No ABR-8611. Ciba-Geigy Corporation. Submitted February 17, 1987.

The results of this analysis indicated that, after oral dosing of rats with Metolachlor, renal excretion of the radiolabel followed first-order kinetics for both the low dose (1.5 mg/kg) and the high dose (300 mg/kg). Low dose kinetics exhibited two components of excretion of ^{14}C-activity, while high dose kinetics exhibited a single component of excretion. No sex differences were noted. Additionally, virtually all of the administered labeled compound was accounted for by the ^{14}C-activity excreted in the urine and in feces.

Reference: Metabolism of CGA 24 705 in the Rat and Addendum to Project 7/74: Metabolism of CGA 24 705 in the Rat, MRID No's. 00015655, 00039193 and 00015425. Study No.'s 7/74 and 12/74. Ciba-Geigy Ltd. Submitted September 26, 1974, November 25, 1975, March 26, 1975.

A separate metabolism study was submitted by the registrant which deals with the identification of the metabolites. The results are summarized below:

Urinary metabolites were identified following oral administration of 28, 33, and 52 mg/kg to male rats. Two metabolites of the organic extractable urinary radioactivity were identified from oral administration of the test compound.

The major metabolic pathway proposed from analysis of urinary as well as fecal metabolites is one of cleavage of the ether bond and subsequent oxidation to the carboxylic acid, as well as hydrolytic removal of the chlorine atom. Conjugation of the parent or metabolites with glucuronic acid or sulfate does not appear to occur.

The aqueous extractable urinary radioactivity contained 58% of the total urinary radioactivity and was composed of 5 different radioactive fractions which were not identified.

This study did not follow current guideline recommendations as to dose levels or the use of both sexes. Therefore, if the metabolic pattern is altered by dose or repeated exposure, this cannot be determined by these data. Further, the doses tested in this study were not equivalent to those tested in the previously discussed study (MRID No. 401144-01). The study is classified as Core-Supplementary Data and does not fulfill the data requirements (§85-1) for a general metabolism study in rats.

The Agency recommends that the registrant provide data on the identification of urinary and fecal metabolites from the submitted study, "Disposition of Metolachlor in the Rat (General Metabolism)" (Ciba-Geigy Corporation, MRID No. 401144-01, Study No. ABR-8611, 2/17/87) to resolve this data gap.

2. Genotoxicity

Reference: Evaluation of Metolachlor Technical in the *in vivo*/*in vitro* Rat Hepatocyte Unscheduled DNA Synthesis Assay, Hazleton Biotechnologies Company, HBC Project No. 20991, August 10, 1988, MRID No. 420433-01.

Under the conditions tested, Metolachlor was inactive in this *in vivo*/*in vitro* rat hepatocyte assay at the dose levels tested (females: 3.07, 31.49, 291.9, and 519.5 mg/kg; males: 2.88, 31.91, 301.03, and 474.5 mg/kg). The study has been classified as Unacceptable and does not satisfy the guideline requirements for a mutagenicity study (§ 84-4) because i) it did not report the batch number or the purity of the test compound and ii) there were no overt signs of toxicity (i.e. dosing could be higher). It was noted that S phase induction was significantly increased in females and only slightly so in males.

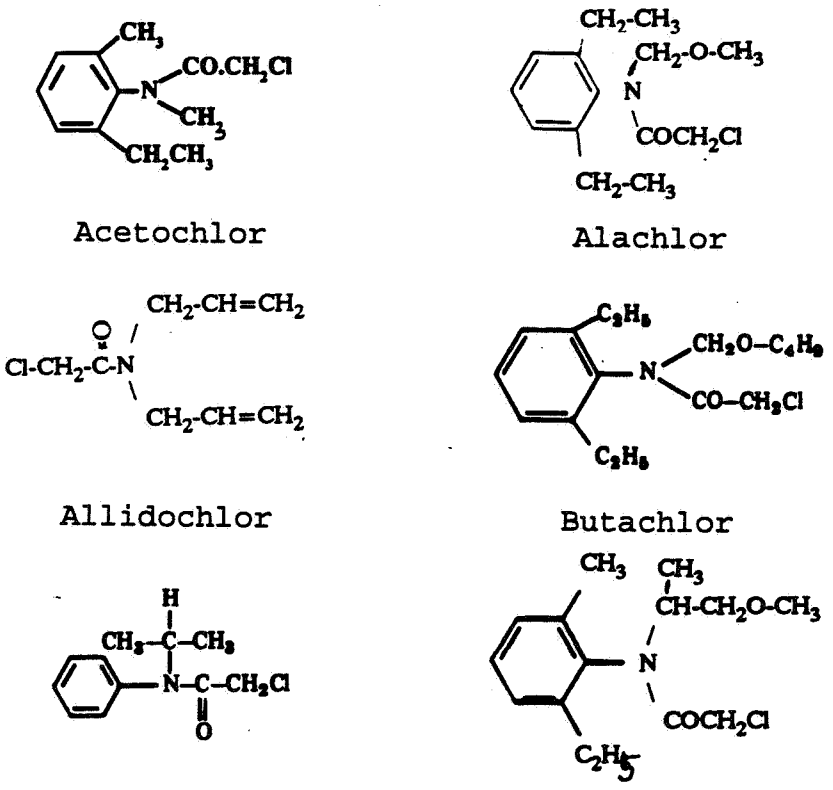
Further discussion about the genotoxicity of Metolachlor can be found in the second peer review document. In general, the PRC did not feel that Metolachlor posed a high degree of risk for genotoxicity; however, they recommended upgrading the *in vivo*/*in vitro* unscheduled DNA test to fulfill the data gap for genotoxicity testing.

3. Structure-Activity Correlations

Metolachlor is structurally related to Acetochlor, Alachlor, Allidochlor, Butachlor, and Propachlor.

Figure 1

Structural Analogs of Metolachlor



Acetochlor has been classified as a Group B2 (Probable Human) Carcinogen by the PRC and the SAP. This was based on the evidence that Acetochlor caused an increased incidence of benign and malignant tumors at multiple sites in Sprague-Dawley rats at 1000 ppm (papillary adenomas of the nasal turbinates in both sexes; hepatocellular carcinomas in both sexes and thyroid follicular cell adenomas in males) and an increased incidence of benign and malignant tumors at multiple sites in Swiss albino CD-1 mice (hepatocellular carcinoma in both sexes at 5000 ppm; lung carcinomas in females at 500, 1500, and 5000 ppm; uterine histiocytic sarcoma and benign ovarian tumors in females at 500, 1500, and 5000 ppm; and a positive trend in kidney adenomas in females). Acetochlor caused point mutations in a Chinese hamster ovary test both with and without metabolic activation, gene mutations in the mouse lymphoma assay (with activation), aberrations in human lymphocytes and unscheduled DNA synthesis (UDS) in an in vivo/in vitro UDS assay. There were no mutagenic

effects in gene mutation tests in bacteria, a micronucleus assay in mice, an in vivo cytogenetics assay in rats and an UDS assay in rat primary hepatocytes in vitro.

The PRC has classified Alachlor as a Group B2 carcinogen. In a dietary study in Long-Evans rats, nasal turbinate tumors were found at 42 mg/kg and squamous cell tumors of the stomach were found in both sexes at 126 mg/kg as well as thyroid follicular adenomas in males at 146 mg/kg. In a dietary study in mice, there was an increased incidence of liver tumors in females at 260 mg/kg. Alachlor was positive in a DNA damage/repair (in vivo/in vitro UDS) assay, while it was negative in bacterial assays, in vivo/in vitro cytogenetics, and a CHO/HGPRT assay. Some metabolites of Alachlor are positive in the Salmonella assay. The registrant used the different rat strain used in the carcinogenicity study as an explanation for the difference in nasal tumor response.

Allidochlor has no acceptable chronic or mutagenicity studies.

Butachlor is carcinogenic in rats after dietary administration, including stomach tumors in females (3000 ppm), adenomas and carcinomas of the nasal mucosa in both sexes (1000 ppm and above), follicular adenomas/carcinomas of the thyroid in females (1000 ppm) and in both sexes at higher levels (3000 ppm), and renal cortical cell tumors in both sexes (3000 ppm). Mice developed alveolar/bronchiolar adenomas/carcinomas at the 2000 ppm level. It was weakly mutagenic in one Salmonella assay, and negative in a bacterial rec (DNA damage) assay and for reversion.

Propachlor showed possible evidence of increased "C" cell tumors of the thyroid and ovarian neoplasia in rats at 500 ppm; however, this study did not test at high enough levels to adequately assess the carcinogenic potential of Propachlor. A carcinogenicity study in mice did not test at high enough levels to adequately assess carcinogenicity potential (500 ppm). Propachlor was positive in a chromosome aberration assay, and suggestive of a positive response in a CHO/HGPRT assay. It was negative in a rat bone marrow cytogenetics assay and in an in vitro UDS assay.

F. Weight of Evidence Considerations:

The Committee considered the following facts regarding the toxicology data on Metolachlor in a weight-of-the-evidence determination of carcinogenic potential.

1. Metolachlor administration resulted in significant dose-related increasing trends in liver neoplastic nodules (adenomas) and combined liver adenomas and/or carcinomas in male rats for both the Hazleton and Hardisty pathology reports. In addition, female rats had significant dose-related increasing trends in liver neoplastic nodules (adenomas) and combined liver adenomas and/or carcinomas for both the Hazleton and Hardisty pathology

reports. There were significant differences in the pair-wise comparisons of the controls with the 3000 ppm dose group for liver adenomas for the Hardisty report and for combined liver adenomas and/or carcinomas for both the Hazleton and Hardisty reports. These tumor incidences were greater than the contemporary historical control range.

2. The PRC agreed that the incidence of nasal tumors in female rats at the HDT was not related to Metolachlor administration at doses of 3000 ppm. However, this dose was determined to be only marginally adequate for evaluation of carcinogenicity. Therefore, the issue of whether Metolachlor would or would not produce nasal tumors cannot be unequivocally resolved.

3. No increase in the incidence of neoplasia was associated with Metolachlor administration in mice.

4. Although the PRC did not feel that Metolachlor posed a high degree of risk for genotoxicity, they recommended repeating the in vivo/in vitro unscheduled DNA test to fulfill the data gap for genotoxicity testing.

5. Metolachlor is structurally similar to Acetochlor and Alachlor, two Group B2 carcinogens with genotoxic activity. The metabolic and biological similarity or dissimilarity of Metolachlor to these compounds has not yet been adequately established. The PRC agreed that the registrant should provide data on the identification of metabolites from the submitted study "Disposition of Metolachlor in the rat (general metabolism)" to resolve issues and fulfill the data requirements.

G. Classification of Carcinogenic Potential:

The PRC considered the criteria contained in the EPA's "Guidelines for Carcinogen Risk Assessment" [FR51: 33992-34003, 1986] for classifying the weight of evidence for carcinogenicity. The PRC agreed that the classification for Metolachlor should be Group C - possible human carcinogen and recommended that, for the purpose of risk characterization, a low dose extrapolation model be applied to the experimental animal tumor data (q_1^*) for quantification of human risk. The q_1^* will be re-calculated based on hepatic neoplasia (combined adenoma and carcinoma) in female rats using the data in the pathology report by Dr. Jerry Hardisty (dated July 20, 1984, Table 4).

The PRC recommended that the registrant perform additional tests in stages. First it was recommended that the in vivo/in vitro unscheduled DNA test be repeated to fulfill the data gap for genotoxicity testing. If this test proves negative, the PRC recommended that the registrant should provide data on the identification of metabolites from the submitted study "Disposition of Metolachlor in the rat (general metabolism)" to resolve issues and fulfill the data requirements. Finally, a comparative metabolism study was recommended in order to provide information on the metabolic generation of quinone imine and

formaldehyde and to support the assertion that the metabolism of Metolachlor is substantially different from its major structurally analogous compounds. After the completion and evaluation of the recommended studies, the PRC agreed to reconsider the weight-of-evidence for the classification of Metolachlor.