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

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MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Peer Review of Metolachlor.
Caswell No. 188D

FROM: Reto Engler, Ph.D.
Chief, Scientific Mission Support Staff
Toxicology Branch
Hazard Evaluation Division (TS-769)

TO: Richard F. Mountfort, Product Manager #23
Registration Division (TS-767)

On May 30, 1985, the Toxicology Branch Peer Review Committee, Dr. Richard Hill (OPTS, Science Advisor), and Dr. Harry Milman (Oncology Branch, OTS) met to discuss and evaluate the data base on Metolachlor, with particular reference to the oncogenic potential of the chemical.

A. Individuals in Attendance:

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

Theodore M. Farber, Ph.D. _____

Richard Hill, M.D. _____

Harry Milman, Ph.D. _____

Louis Kasza, D.V.M.,Ph.D. _____

Herbert Lacayo, Ph.D. _____

John A. Quest, Ph.D. _____

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

Gary Burin, M.P.H. _____

D. Steven Saunders, Ph.D. _____

Laurence D. Chitlik, D.A.B.T. _____

B. Material Reviewed:

The material available for review consisted of DER's of rat and mouse chronic oncogenicity bioassays, laboratory audit reports and related memoranda on the bioassay, risk assessment information, data on other toxicology studies (mutagenicity, subchronic, and reproduction/teratology tests), and a listing of one-liners on the Metolachlor data base. A copy of the material reviewed is appended to this panel report.

C. Overview of Toxicology Issues:

Metolachlor was observed to produce primary liver tumors (neoplastic nodules plus hepatocellular carcinomas combined) in female rats at the highest dose level tested in two separate chronic feeding studies sponsored by the registrant, Ciba Giegy Corp.

The initial rat chronic bioassay was performed at Industrial Biotest Laboratories (IBT) and was classified as "supplementary" data. A repeat rat chronic bioassay was performed at Hazelton-Raltech, Inc., and was classified as "CORE minimum" data. Although both studies were given careful consideration, the Peer Review Committee focused attention primarily on data in the Hazelton-Raltech rat study because of the "CORE minimum" classification.

The registrant also evaluated the oncogenic potential of Metolachlor in two mouse oncogenic feeding studies. One of the studies was performed at IBT, and a repeat study was performed at Hazelton-Raltech, Inc. Both mouse studies were classified as "CORE minimum" data, and no evidence for oncogenicity was found in either mouse study.

D. Evaluation of the Evidence:

1. Rat Chronic Studies

a) Initial IBT Study: In the IBT rat study (No. 622-07925 the following incidence pattern of liver hyperplastic (i.e., neoplastic) nodules, cystic cholangiomas, carcinomas, and other tumors occurred in female rats receiving Metolachlor in the feed for 2 years.

Dose (ppm)	0	30	300	1000	3000
Number of Female Examined (final sacrifice)	54	58	60	60	60
Hypertrophic-Hyperplastic Nodules	1	1	3	3	9
Angiosarcoma	0	0	0	0	1
Cholangioma	0	0	1	0	0
Cystic Cholangioma	2	2	1	2	6
Carcinoma	0	0	0	0	2
Total (No. Animals with primary liver tumors)	3	3	5	5	15*

(*Three animals each bore two primary liver tumors.)

An increase in primary liver tumors was found in high dose female rats. In this study, hyperplastic nodules were included as an oncogenic response along with cystic cholangioma and carcinoma based on recommendations of the National Cancer Institute (Cancer Res. 35:3214-3223, 1975) and the National Academy of Science (J. NCI 64: No. 1, p. 185, 1980). This was the only oncogenic response observed in female rats. No statistically significant increase in the incidence of primary liver tumors was observed in male rats administered the same dose levels, although a slight positive trend was apparent. This IBT study was classified as "supplementary" data due to inadequate clinical chemistry determinations and dietary preparation records.

b) Repeat Hazelton-Raltech, Inc., Study: In this study (No. 80030) the following incidence pattern of liver neoplastic nodules and carcinomas occurred in female rats receiving Metolachlor in the feed for 2 years.

Dose (ppm)	0	30	300	3000
No. Females	60	60	60	60
Neoplastic Nodules	0	1	2	6*
Carcinomas	0	0	0	1
Total No. animals with proliferative lesions	0	1	2	7**

* ($P < 0.05$) ** ($P < 0.01$)

A significantly increased incidence of proliferative hepatic lesions was found in high dose females at terminal sacrifice. The survival of the animals at 24 months was 54%, 57%, 42% and 57% for the control, low, mid and high dose groups. This was the only oncogenic response observed in female rats. No statistically significant increase in proliferative hepatic lesions was observed in male rats administered the same dose levels; however, there was a trend of increasing neoplastic nodules (1/60, 1/60, 0/60 and 4/60 at control, low, mid and high dose) in male rats but this was not the case for carcinomas (2/60, 1/60, 3/60 and 3/60 at control, low, mid and high doses) in males. When the incidence of these lesions was combined, no statistically significant effect was noted, although a trend was demonstrated (i.e. 3/60, 2/60, 3/60 and 7/60 at control, low, mid and high doses. This study was classified as "Core minimum".

2. Mouse Chronic Studies:

a) Initial IBT Study: A 2-year mouse study (No. 622-07925) using dietary levels of metolachlor of 0, 30, 1000 and 3000 ppm was reviewed and classified as "CORE minimum." No oncogenic effects were noted. The Review Committee did not raise any issues concerning the results of this bioassay.

b) Repeat Hazelton-Raltech, Inc. Study: A 2-year mouse study (No. 79020) using dietary levels of Metolachlor of 0, 300, 1000 and 3000 ppm was reviewed and classified as "CORE minimum." No oncogenic effects were noted. The highest dose level tested produced a reduction in weight gain ($P < 0.05$) in male and female mice indicating that the MTD was approximated. A slight reduction in survival was also noted in high dose females (34.6% survival to end of test vs. 53.8% controls, 38.5% low dose and 46.2% mid dose) which might have been related to Sendai virus infections early in the study. The review committee had no issues concerning the results of this bioassay.

3. Mutagenicity Assays

Two genotoxicity assays were performed with Metolachlor, a mouse dominant lethal study and a Ames mutagenicity assay. Both tests were acceptable and Metolachlor was not mutagenic in either study.

4. Teratology and Reproduction Studies:

Four pivotal studies were briefly considered by the Committee: 1) Metolachlor was not teratogenic, fetotoxic, or maternally toxic at the highest dose tested (360 mg/kg/day) in a teratology study in rats (Ciba Giegy, CORE minimum); 2) Metolachlor was not teratogenic or fetotoxic at the highest dose tested (360 mg/kg/day) in rabbits, but produced maternal toxicity (lacrimation, miosis, decreased food consumption, and reduced day 12 and 18 body weights) at this dose level (Argus, CORE minimum); 3) in a 2-generation study in rats, the highest dose level (1000 ppm) reduced pup weights and parental food consumption (Toxigenics, CORE guideline); and 4) in a 3-generation study in rats the highest dose level tested (1000 ppm) was a NOEL (IBT, supplementary).

D. Weight of Evidence Considerations:

The Committee considered the following facts regarding toxicology data on Metolachlor to be of importance in a weight of the evidence determination of oncogenic potential.

1. Metolachlor was associated with a significantly elevated incidence of proliferative liver lesions (neoplastic nodules plus carcinomas combined) at the highest dose level tested (3000 ppm in the diet) only in female rats. A non significant trend of increasing neoplasic nodules was observed in male rats in both rat studies. No proliferative lesions were noted in female or male mice.

2. The significantly elevated incidence of proliferative liver lesions observed in high dose female rats (i.e., 7/60) was primarily due to the occurrence of neoplastic nodules (i.e., 6/60) rather than to hepatocellular carcinomas per se (i.e., 1/60). There was no apparent difference in the time-to-occurrence of the proliferative lesions (i.e., almost all liver tumors were observed at terminal sacrifice).

3. Historical control data on the proliferative liver lesions in the same strain of rat (at Hazelton-Raltech, Inc.) is available from one other study in which two control groups were employed. The incidence of these proliferative lesions were 0/46 and 1/46 for females of the two control groups.

4. The hepatic proliferative responses observed in female rats appear to be repeatable, since a similarly elevated incidence of neoplastic nodules was observed in female rats at the same dose level tested (i.e., 3000 ppm) in both the initial IBT study and the subsequent Hazelton-Raltech, Inc. study. However, as noted above, a statistically significant oncogenic response was not produced in male rats in either study at the same maximum dose level.

5. Metolachlor was not mutagenic in two genotoxicity studies performed on the compound (mouse dominant lethal study and Ames mutagenicity assay) nor were teratogenic, fetotoxic or adverse reproductive effects observed in studies in rats or rabbits.

6. Preliminary 90-day animal toxicity studies indicated that a dose of 3000 ppm did not exceed a "maximum tolerated dose" (MTD) in those subchronic tests. However, in the chronic rat bioassay, the dose of 3000 ppm appeared to approximate the MTD level as it did not adversly affect the survival of the animals but was associated with: (a) weight loss in female rats ($P < 0.05$) from study weeks 2 to 104 (which was found to be reversible following discontinuation of compound administration for one month in a satellite group of female rats after 12 months on test); (b) reduced food consumption in female rats ($P < 0.05$) at intermittent intervals throughout the study; (c) testicular atrophy with degeneration of tubular epithelium in male rats upon histological examination (the severity of the effect was similar in all treated groups but the time of onset was sooner in all groups of treated males); and (d) 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.

7. Metolachlor bears a structural resemblance to Alachlor but differs from Alachlor in toxicity and in some physical properties. Available metabolism data indicates that both Metolachlor and Alachlor are metabolized to analine derivatives. However, adequate data is not available for Metalachlor. Nonetheless, types of oncogenic responses produced by Metolachlor (proliferative liver lesions) and Alachlor (nasal turbinate, stomach and thyroid tumors) in rats are different.

E. Classification of Oncogenic Potential:

The Committee concluded that the data available for Metolachlor provides weak evidence of carcinogenicity. Before making a final conclusion on the oncogenic potential of Metolachlor, the Committee recommended that the registrant provide: (1) the full mutagenicity battery required by EPA; and (2) metabolism studies as required by the 1982 guidelines. Subsequent to receipt of this information, the Committee will reconvene to consider classification of the oncogenic potential of the chemical and possible recalculation of the Q-star (potency factor).

Addendum:

Dr. Saunders provided the following additional information to this report on 7/30/85: (1) Data for histopathologic examination of nasal tubinates, from control and high dose male and female rats in the chronic feeding study, were recently submitted and are currently under review; (2) An *in vivo* cytogenetics study and two *in vitro* DNA repair studies were recently submitted and are currently under review.

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