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

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AUG 0 3 1992

MEMORANDUM

OFFICE OF PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Atrazine - re-evaluation of the maternal toxicity in the rabbit teratology study (MRID # 405663-01). Tox Chem.# 63

TO: George Ghali, Ph.D.
RfD/Mini Peer Review Committee
SACB/HED (H7509C)

FROM: Stephen C. Dapson, Ph.D. Stephen C. Dapson 4/17/92
Senior Pharmacologist, Review Section I
Toxicology Branch II/HED (H7509C)

THRU: Yiannakis M. Ioannou, Ph.D., D.A.B.T. Y.M. Ioannou 4/
Section Head, Review Section I

ACTION REQUESTED: The HED-RfD Peer Review Committee requested the re-evaluation of the maternal toxicity in the rabbit teratology study with atrazine (A Teratology Study of Atrazine Technical in New Zealand White Rabbits, Report No. 68-84, 9/18/84, MRID # 405663-01).

CONCLUSIONS: For the rabbit teratology study with atrazine (A Teratology Study of Atrazine Technical in New Zealand White Rabbits, Report No. 68-84, 9/18/84, MRID # 405663-01), maternal toxicity was noted in the high dose group only. From the body weight gain data, it is not apparent that there was a dose related decrease in body weight gain at all dose levels as originally reported. A treatment related effect is noted in the body weight gain in the high dose group during the dosing period with a rebound increase in body weight gain following the dosing period. Combined dosing period and post dosing period body weight gain for the high dose group also shows a decrease as does the corrected body weight gain for the high dose group. Food consumption data for these periods also supports the observation of a high dose group effect. Low food efficiency was noted in the high dose group during the dosing period and for the combined period including the dosing period and post dosing period. There appears to be increased food efficiency in the post dosing period which supports what was noted for food consumption and the rebound in body weight gain in the post dosing period. Other signs of maternal toxicity related to clinical observations which included an increase in "stool: little, none and/or soft" in the high dose

group along with the evidence of "blood on vulva/in cage" in the high dose group. No treatment related signs were noted in the low or mid dose groups. Cesarean section data showed no additional maternal toxicity data; however, developmental toxicity was noted at the high dose in the form of increased total resorptions and resorptions per dam, decreased total live fetuses and live fetuses per dam (litter size), an increased post-implantation loss and a decrease in mean fetal weight.

Therefore:

MATERNAL TOXICITY NOEL = 5 MG/KG/DAY
MATERNAL TOXICITY LOEL = 75 MG/KG/DAY

NOTE: The NOEL for maternal toxicity may be higher than the established 5 mg/kg/day due to the inordinate spread of doses used in this study (1, 5 and 75 mg/kg/day).

2

DISCUSSION

The maternal toxicity conclusions from the DER (Document No.s 006761 and 006131) for "A Teratology Study of Atrazine Technical in New Zealand White Rabbits" (Ciba-Geigy, Project No. 68-84, 9/18/84, MRID No. 405663-01) are as follows:

> It is concluded that the teratogenicity study of atrazine in rabbits (Safety Evaluation Facility, CIBA-GEIGY Corp., # 68-84) demonstrates the following:
>
> Maternal No Observed Effect Level (NOEL): 1 mg/kg/day
> Maternal Lowest Observed Effect Level (LOEL): 5 mg/kg/day
>
> These values are based on a statistically significant reduction in body weight gain for gestational days 14-19 and a statistically significant reduction in food consumption on gestational days 17 and 19 in the 5 mg/kg/day group.

Attached Tables 4 and 6 were used to support the above findings; however, total mean body weight was considered rather than body weight gain; therefore the following table presents body weight gain for specific gestational periods extracted from the original report:

Body Weight Gains (grams)[a]

DAYS:	Prior to Dosing Period 0-7	Dosing Period 7-19	Post Dosing Period 19-29	Dosing plus PostPeriod 7-29	Corrected Body Weight Gains[1] 7-29
Control	185	233	93	326	-259
LDT	174	181	108	289	-287
MDT	166	108	152	260	-308
HDT	182	-726	558	-168	-576

[1] = corrected body weight gain = body weight gain for dosing period plus post dosing period minus gravid uterus weight (in this case uterus plus placenta and fetuses).

[a] = Data extracted from Report No.68-84, Table 4.

From the above body weight gain data, it would be apparent that there was a dose related decrease in body weight gain at all dose levels; however, this is a questionable conclusion considering that the rabbits weighed 7 to 11 lbs (3.8 to 4.0 kg) at the beginning of the study and weighed 4.0 to 4.4 kg at the end of the study, a small change in body weight is not necessarily related to toxicity of the compound but rather normal fluctuations seen in an animal's growth. A treatment related effect is noted

in the body weight gain in the high dose group during the dosing period with a rebound increase in body weight gain following the dosing period. Combined dosing period and post dosing period body weight gain for the high dose group also shows a decrease as does the corrected body weight gain for the high dose group. An inspection of the supplied individual animal data also supports the conclusion that normal growth was observed in the low and mid dose groups with only the high dose group having animals apparently affected by treatment. It is also apparent that several of the animals in the control group were of a higher starting body weight than those of the low and mid dose groups.

The following tables present food consumption data for specific gestation periods calculated as mean gram/day from individual daily food consumption in mean grams and food efficiency data calculated from the body weight gain data and food consumption data:

Food Consumption Data (mean g/day)[a]

	Prior to Dosing Period	Dosing Period	Post Dosing Period	Dosing plus PostPeriod
Control	194	182	121	155
LDT	187	164	111	140
MDT	196	162	114	140
HDT	207	15	144	74

[a] = Data extracted from Report No. 68-84, Table 2.

Food Efficiency Data (%)

	Prior to Dosing Period	Dosing Period	Post Dosing Period	Dosing plus PostPeriod
Control	13.6	10.7	7.7	9.6
LDT	13.3	9.2	9.7	9.4
MDT	12.1	9.2	13.3	8.4
HDT	12.6	-403.3	38.8	-10.3

Food efficiency is expressed as body weight gain over a given time period in grams divided by the food consumption in grams over the same time period X 100. This calculation gives the percentage efficiency with which the animal converts food for maintenance. Low efficiency compared with controls indicates toxicity in the consuming animals.

The food consumption data for these periods also supports the observation of a high dose group effect. Low food efficiency was noted in the high dose group during the dosing period and for the combined period including the dosing period and post dosing period. There appears to be increased food efficiency in the post dosing period which follows what was seen for food consumption and the rebound in body weight gain in the post dosing period. The variability in the data is most likely related to the "picky" feeding habits of rabbits, also the time of day of dosing was not provided, which, if prior to the animal's normal feeding time, could affect the food consumption.

Other signs of maternal toxicity were related to clinical observations as seen on the following table from the investigators report:

Observations	Dose (mg/kg)			
	0	1	5	75
Stool: little, none and/or soft	9/19[2]	4/19	10/19	19/19**
Blood on Vulva/in Cage	0/19	1/19	0/19	4/19*
Vasodilation of Ears	0/19	0/19	0/19	1/19
Decreased Motor Activity	0/19	0/19	0/19	1/19
Alopecia	5/19	3/19	2/19	9/19
Lacrimation	3/19	0/19	1/19	3/19
Scab	1/19	1/19	2/19	0/19
Nasal Discharge	1/19	0/19	0/19	0/19
Abortion	0/19	0/19	1/19	2/19
Death	0/19	3/19[1]	0/19	0/19

*Different from the control group at $p \leq 0.05$.

**Different from the control group at $p \leq 0.01$.

[1]Females CT11 and CT15 of the 1 mg/kg group died on days 17 and 26 of gestation, respectively. Female CU18 of the 1 mg/kg group died on day 19 of gestation, the apparent result of an intubation accident.

[2]Female CV16 of the control group was not included in the statistical analysis (Appendix 2) as observation occurred during the pre-dosing period.

The increase in "stool: little, none and/or soft" in the high dose group along with the evidence of "blood on vulva/in cage" in the high dose group (although each group of signs are technically combined but related observations), they are indicative of maternal toxicity. No treatment related signs were noted in the low or mid dose groups.

The following table presents the cesarean section data[a]:

Dose:		Control	LDT	MDT	HDT
#Animals Assigned		19	19	19	19
#Animals Inseminated		19	19	19	19
#Animals Pregnant		16	17	16	18
Pregnancy Rate (%)		84.2	89.5	84.2	94.7
Maternal Wastage					
#Died		0	3	1	2
#Died/pregnant					
#Non pregnant		3	2	3	1
#Aborted					
#Premature Delivery					
#Animals with litters		16	14	15	15
Total Corpora Lutea		218	184	194	214
Corpora Lutea/dam		13.6	13.1	12.9	14.3
Total Implantations		161	143	157	166
Implantations/Dam		10.1	10.2	10.5	10.4
Total Resorptions		21	19	21	77
Resorptions/Dam		1.3	1.4	1.4	4.8**
Total Live Fetuses		140	124	136	89
Live Fetuses/Dam		8.8	8.9	9.1	5.9*
Total Dead Fetuses		0	0	0	0
Mean Fetal Weight (gm)	M	46.04	43.99	43.21	35.67**
	F	44.00	43.25	43.06	35.80**
Preimplantation Loss(%)		26.1	21.6	18.4	26.5
Postimplantation Loss(%)		12.0	11.4	13.0	42.6**
Sex Ratio (% Male)		48.6	47.6	44.1	51.7

* = $p < 0.05$; ** = $p < 0.01$

a = Data extracted from Report No. 68-84, Table 5 and Appendices.

The above data showed no additional maternal toxicity; however, developmental toxicity was noted at the high dose in the form of increased total resorptions and resorptions per dam, decreased total live fetuses and live fetuses per dam (litter size), an increased post-implantation loss and a decrease in mean fetal weight.

CHEMICAL: ATRAZINE
PC CODE: 080803
CASWELL #: 063

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83-3(b)
Developmental Toxicity Study MRID No. 405663-01
Species: rabbit
Ciba Geigy Pharmaceutical, Eng.
68-84; 9/18/84

Entry for maternal toxicity should be changed to the following:

Maternal NOEL = 5 mg/kg/day. Maternal LEL=75 mg/kg/day (decrease body weight gain, low food efficiency, increase in "stool: little, none and/or soft", and "blood on vulva/in cage")

Note: The NOEL for maternal toxicity may be higher thatn the established 5 mg/kg/day due to the inordinate spread of doses used in this study.

7

U.S. ENVIRONMENTAL PROTECTION AGENCY
OFFICE OF PESTICIDES/HED/SACB
TOX ONELINERS

TOXCHEM NO. 063- Atrazine FILE LAST PRINTED: 01/16/92

CITATION	MATERIAL	ACCESSION/ MRID NO.	RESULTS	TOX CAT	COREGRADE/ DOCUMENT#
83-3(a) Developmental Toxicity Study Species: rat Ciba Geigy, N.J. 882049; 2/23/89	Atrazine (purity unknown) Batch FL 841802	410652-01 416864-01	Atrazine was admin. orally to 25 Sprague-Dawley rats/group at: 0, 5, 25, or 100 mg/kg/d during gest. days 6-15, inclusive. Maternal NOEL = 25 mg/kg/d. Maternal LOEL = 100 mg/kg/d., based on decr. food consumption & body weight gain. Fetotoxic NOEL = 25 mg/kg/d. Fetotoxic LOEL = 100 mg/kg/d., based on incr. delayed ossification of skull bones. Core Clasification: Supplementary; this study may be reclassified if the purity of the test material is provided.		Supplementary 008493
83-3(b) Developmental Toxicity Study Species: rabbit Ciba Geigy Pharmaceutical, Eng 68-84; 9/18/84	Atrazine Tech. 96.3%	~~254979~~ 405663-01	Maternal NOEL = 1 mg/kg/day. Maternal LEL = 5 mg/kg/day. (reduced body wt. gain & red. food consump). Develop. NOEL = 5 mg/kg/day. Develop LEL = 75 mg/kg/day (incr. resorptions, decr. fetal wts of male & female pups, delayed ossification of appendages). A/D ratio = 0.2 (1/5) Doses: 0, 1, 5, 75 mg/kg/d in N.Z.W. str by gavage on 7-19d gestation.		Supplementary 006131 Minimum 006761 006937
83-4 Reproduction-3 generation Species: rat Woodard Research 1966	Atrazine 80W	00024471	Systemic NOEL > 100 ppm (HDT) ; Reproductive NOEL > 100 ppm (HDT) Levels tested : 0,50,100 ppm		Supplementary 002917 000525
83-4 Reproduction-2 generation Species: rat Ciba Geigy Pharmaceutical, Eng 852063; 11/17/87	Atrazine Tech.	404313-03	Dosage levels: 0, 10, 50, 500 ppm. Parental NOEL = 50 ppm Parental LEL = 500 ppm based upon decr. body wts, body wt. gain, and food consumption in both parents and females throughout the study. In addition the increase in relative testes weight seen in parental males could be treatment related since it was seen in both generations. Reproductive NOEL = 10 ppm. Reprod. LEL = 50 ppm based upon decr. body weights of pups of the second generation on postnatal day 21.		Minimum 006718 006937
Feeding-14 day Species: rat Hazleton Lab America 483-268; 03/06/90	Atrazine 97.4%	415709-01	Atrazine and Diaminochlorotriazine (DACT) dosed at: 0, 100, 200 & 400 mg/kg/day. High dose for both compounds changed to 300 mg/kg/day after day 4. Treated group showed reduced body weight/body weight gain. All treated animals thin, hunched appearance. Estrogen lower => 200 mg/kg, atrazine and DACT. Progesterone lower at => 200 mg/kg DACT. LH and prolactin lower in 100 and 200 mg/kg DACT Study is not upgradeable.		Supplementary 008723
82-1(b) Feeding-3 month Species: dog WARF Inst. T 635; 1977	Atrazine Tech.	00163339	Tested at 0, 200, 632, 2000 ppm in diet (0, 5, 15.8, 50 mg/kg/day) in beagles. NOEL < 200 ppm (5 mg/kg/day) (LDT), (based on body weight gain depression in males). In addition at 623 ppm and above in males there was a slight decr. in RBC, HCT and HgB. There was also a mild to total arrest of spermatogenesis. At 2000 ppm in males, there was decr. food consumption; in females, there was body wt. loss, decr. food consumption and a slight decr. in RBC, HcT and HgB.		Supplementary 006937 Supplementary 006938