



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

JUN 11 1996

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Atrazine/Hydroxyatrazine: Recommendation Regarding Need
for RfD Peer Review Committee Meeting on Atrazine;
Assignment of RfD for Hydroxyatrazine

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FROM: Edwin R. Budd, Acting Section Head
Review Section III
Toxicology Branch I
Health Effects Division (7509C)

Budd
6/6/96

TO: William Burnam, Chief
Science Analysis Branch
Health Effects Division (7509C)

THRU: Karl Baetcke, Ph.D., Chief
Toxicology Branch I
Health Effects Division (7509C)

K/B
6/7/96

RECOMMENDATION

On June 3, 1996, Joycelyn Stewart, Melba Morrow, Kit Farwell and Edwin Budd of Toxicology Branch I met to discuss the need for a RfD Peer Review Committee (PRC) meeting on atrazine. Based on a consideration of all available subchronic and chronic studies on atrazine and its metabolites, as summarized in the attached Toxicology Profile by Edwin Budd, it was unanimously agreed that no new toxicological data had been submitted since the last RfD PRC meeting in December, 1992 that would warrant a re-assessment of the RfD for atrazine at this time. Although several 1- or 2-year long-term studies on atrazine had been evaluated since the last RfD PRC meeting, the NOEL in none of these studies was significantly lower than that determined in the study on which the RfD is presently based. Regarding possible alterations in hormone levels, it was agreed that the available data did not adequately support basing the RfD for atrazine on alterations in hormone levels, if any, at this time. The meeting participants recommend that the RfD for atrazine remain unchanged from its current value of 0.035 mg/kg/day, which is based on a NOEL of 3.5



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mg/kg/day determined in a 2-year combined feeding/carcinogenicity study in Sprague-Dawley rats using technical grade atrazine as the test material (MRID 00141874, 00157875, 00158930, 40629302). UF = 100.

In accordance with the recommendation of the HED Metabolism PRC, an RfD for hydroxyatrazine (G-34048) was also recommended by the meeting participants. It is anticipated that this RfD will be used to conduct risk assessments for dietary exposures to the hydroxyatrazine metabolite, which is a major plant and soil metabolite, but is not an animal metabolite. Based on a consideration of the available subchronic and chronic studies on hydroxyatrazine, as summarized in the Toxicology Profile, the meeting participants recommend that a RfD for hydroxyatrazine be established at 0.01 mg/kg/day, based on a NOEL of 1.0 mg/kg/day determined in a 2-year combined feeding/carcinogenicity study in Sprague-Dawley rats using technical grade hydroxyatrazine as the test material (MRID 42662901, 43314301, 43532001). UF = 100. It is noted that 4 subchronic/chronic studies using hydroxyatrazine as the test material were available for consideration (a 90-day feeding study in rats, a 90-day feeding study in dogs, a 2-year combined feeding/carcinogenicity study in rats, and a developmental toxicity study in rats). The meeting participants agreed that it should not be necessary for the RfD PRC to convene at this time to confirm the RfD for hydroxyatrazine.

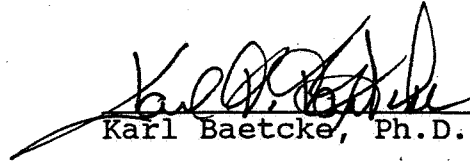
Regarding toxic effects and NOELs observed in studies on the atrazine chlorometabolite, diaminochloroatrazine (DACT, G-28273), the meeting participants felt that the results in the available subchronic/chronic studies (a 90-day feeding study in rats, a 13/52-week feeding study in dogs, and a developmental toxicity study in rats) did not engender toxic concerns necessitating changes in the present risk assessment methodologies for atrazine, particularly since DACT, in addition to being a major plant metabolite, is also a major animal metabolite (26% of the administered dose in rats).

Further studies on additional atrazine chlorometabolites (G-28279 and G-30033) included for each metabolite a 90-day study in rats, a 90-day study in dogs, and a developmental toxicity study in rats. Both of these metabolites are minor atrazine metabolites in plants and in animals. The meeting participants agreed that the results in these studies would not be expected to affect the RfD for atrazine or hydroxyatrazine.

It should be noted that some of the studies referred to in this memorandum have not yet been reviewed by EPA and the results presented in this memorandum are those of the study author. Also, some other studies have been reviewed only by the contractor at this time and are presently awaiting secondary review and approval by EPA. These studies are clearly identified in the attached Toxicology Profile.

CONCURRENCE

I concur with the meeting participants recommendations (1) that it is not necessary at this time to re-assess the RfD for atrazine, and (2) that the RfD for hydroxyatrazine be established at 0.01 mg/kg/day.


Karl Baetcke, Ph.D.

cc: Joycelyn Stewart (TB-1)
Melba Morrow (TB-1)
Kit Farwell (TB-1)
George Ghali (SAB)
Rick Whiting (SAB)
Steve Schaible (SAB)
Kathryn Boyle (RCAB)
John Abbotts (Chem II)
Dave Jaquith (OREB)
Jim Carleton (OREB)

TB596:ATRAZI05.066

TOXICOLOGY PROFILE

Subchronic, Chronic, Developmental
and Reproductive Toxicology Studies

for

Atrazine (G-30027)

Hydroxyatrazine (G-34048)

Diaminochlorotriazine (DACT, G-28273)

G-28279

G-30033

by

Edwin R. Budd

June 4, 1996

TB596:ATRAZI06.066

Atrazine Technical
Subchronic Toxicity

Guide- line	Study Ident & Class	Results
82-1(b)	90-Day Feeding in Dogs WARF Institute Study T-635 Study init on 1/12/77 Tisdell and Harris MRID 00163339 Doc. 006938 <u>Supplementary</u>	<u>Males</u> NOEL < 5 mg/kg/day (LDT) LOEL = 5 mg/kg/day based on decr body weight gain. At 15.8 mg/kg/day, also decr RBC, Ht and Hg; decr spermatogenesis. At 50 mg/kg/day, also decr food consumption. <u>Females</u> NOEL = 15.8 mg/kg/day LOEL = 50 mg/kg/day based on decr body weight gain; decr food consumption; decr RBC, Ht and Hg. <u>Doses:</u> 0, 200 632 or 2000 ppm in the diet (0, 5, 15.8 or 50 mg/kg/day) to Beagle dogs.
82-2	21-Day Dermal in Rabbits Ciba-Geigy Corp. Study 882035 December 1, 1989 Huber, K.R. MRID 42089902 Doc. 010683 Guideline	<u>Systemic Toxicity</u> NOEL = 100 mg/kg/day LOEL = 1000 mg/kg/day based on decr body weight gain, decr food consumption, incr spleen weights, few/mucoid feces, decr RBC & HT (F only), decr total pro- tein & chloride (M only), incr cholesterol & triglycer (F only). <u>Dermal Irritation</u> NOEL = 100 mg/kg/day LOEL = 1000 mg/kg/day based on acanthosis, hyper- keratosis, focal inflammation, erythema, scaling of treated skin. <u>Doses:</u> 0, 10, 100 or 1000 mg/kg/ day dermally to New Zealand rabbits for 25 days (6 hours/day).

Atrazine Technical

Chronic Toxicity

Guide- line	Study Ident & Class	Results
83-1(a)	2-Year Combined	<u>Males</u>
83-2(a)	Feeding/Oncogenicity in Sprague Dawley Rats American Biogenics Study 410-1102 April 29, 1986 Mayhew et al.	NOEL = 3.5 mg/kg/day LOEL = 25 mg/kg/day based on decr body weight gain. At 50 mg/kg/day, also incr degen of rectus femoris muscle. Negative for carcinogenicity.
	MRID 00141874, 00157875 00158930, 40629302 Doc. 004453, 005940	<u>Females</u> NOEL = 3.5 mg/kg/day LOEL = 25 mg/kg/day based on decr body weight gain. At 50 mg/kg/day, also decr survival; decr RBC, Ht, Hg; incr retinal degen; incr liver necrosis; incr degen of rectus femoris muscle. <u>Positive</u> <u>carcinogenic response in mammary</u> <u>gland.</u> At 2 years, incr carcinomas at 3.5, 25 and 50 mg/kg/day, incr fibroadenomas/adenomas at 50 mg/kg/day; incr (all) mammary tumors at 25 and 50 mg/kg/day.
	Minimum for chronic feeding and for oncogenicity	
	<u>Study on which the</u> <u>RfD is presently</u> <u>based (as of June,</u> <u>1996).</u>	
		<u>Doses:</u> 0, 10, 70, 500 or 1000 ppm in the diet (0, 0.5, 3.5, 25 or 50 mg/kg/day) to Sprague Dawley rats.
83-1(a)	1-Year Combined	<u>Author's Conclusions--Under Review</u>
83-2(a)	Feeding/Oncogenicity in Female Sprague Dawley Rats Ciba-Geigy Corp. Study F-00171 December 8, 1995 Pettersen and Turnier	<u>by EPA (May, 1996)</u>
	MRID 43598623, 43934402 Doc. (under review)	<u>Females (only)</u> NOEL sl < 4.1 mg/kg/day (occas sl decr body weight gain) LOEL = 23.9 mg/kg/day based on decr body weight gain, marginal decr food consumption & decr feed efficiency.
	Not yet classified <u>Limited Histopath</u>	Only pituitary gland, mammary gland, ovaries, uterus, vagina, estrous cycle, and various hormone levels exam. <u>Positive</u> <u>carcinogenic response in mammary</u> <u>gland.</u> At 23.9 mg/kg/day (at 1

Atrazine Technical
Chronic Toxicity (Continued)

year), incr incid of (total comb) mammary tumors and decr onset time (latency period) for certain comb of mammary tumors.

Doses: 0, 15, 30, 50, 70 or 400 ppm in the diet (0, 0.8, 1.7, 2.8, 4.1 or 23.9 mg/kg/day) to female CD (Sprague Dawley) rats. Interim sacrifices at 3, 6 and 9 months.

83-1(b) 1-Year Chronic
Feeding in Dogs
Ciba-Geigy Corp.
Study 852008
October 27, 1987
O'Connor, D. et al.

MRID 40431301, 41293801
Doc. 006718, 007647

Minimum

Males

NOEL = 5.0 mg/kg/day

LOEL = 34 mg/kg/day

based on death, cachexia, ascites, decr body weight gain, decr food consumption, EKG changes (irreg heart beats, incr heart rate, decr p-II value, atrial premature complexes, and atrial fibrillation), cardiac lesions (dilation of atria and atrial degeneration).

Females

NOEL = 5.0 mg/kg/day

LOEL = 34 mg/kg/day

based on same effects as males.

Doses: 0, 15, 150 or 1000 ppm in the diet (0, 0.5, 5.0 or 34 mg/kg/day) to beagle dogs.

83-2(a) 2-Year Oncogenicity
in Fischer 344 rats
Hazleton Washington
Study HWA 483-277
February 18, 1992
Thakur, A.K.

MRID 42227001
Doc. 010771, 010705

Guideline for
oncogenicity

Males

NOEL = 3.4 mg/kg/day

LOEL = 9.9 mg/kg/day

based on decr body weight gain (weeks 0-76).

At 20.2 mg/kg/day, also decr food consumption throughout study.
Negative for carcinogenicity.

Females

NOEL = 4.4 mg/kg/day

LOEL = 12.7 mg/kg/day

based on decr body weight gain (weeks 0-76)

At 26.2 mg/kg/day, also

Atrazine Technical
Chronic Toxicity (Continued)

	"thinness"; decr food consumption (weeks 1-13). Negative for carcinogenicity.
	<u>Doses</u> : 0, 10, 70, 200 or 400 ppm in the diet (0, 0.5, 3.4, 9.9 or 20.2 mg/kg/day in males; 0, 0.6, 4.4, 12.7 or 26.2 mg/kg/day in females) to Fischer 344 rats.
83-2(a) Lifetime (123-126 Weeks) Oncogenicity in Fischer 344/LATI Rats Pinter, A. et al. (1990) Neoplasma 37, pp. 533-544. (IARC Study, performed in Hungary)	<u>IARC's Conclusions</u> *--Not Reviewed by EPA * IARC Monographs on the Eval of Carcinogenic Risks to Humans (1991) 53, p. 450.
MRID (none) Doc. (none)	<u>Males</u> At 37.5 mg/kg/day, stat sig incr incid of mammary gland tumors (1/48, 1/51, 9/53, including 1 carcinoma).
Not classified	<u>Females</u> At 37.5 mg/kg/day, stat sig incr incid of uterine adenocarcinomas (6/45, 8/52, 13/45) and of leukemias and lymphomas combined (12/44, 16/52, 22/51). <u>Doses</u> : 0, 500 or 1000 ppm (0, 25 or 50 mg/kg/day) for 8 weeks, then due to toxicity reduced to 0, 375 or 750 ppm (0, 18.8 or 37.5 mg/kg/day) for remainder of study.
83-2(a) 2-Year Oncogenicity in Female Sprague Dawley Rats Hazleton Washington Study HWA 483-275 January 27, 1992 Thakur, A.K.	<u>Females (only)</u> NOEL = 3.8 mg/kg/day LOEL = 23 mg/kg/day based on decr body weight gain (weeks 0-76); sl decr (neg trend) survival (equivocal). <u>Positive carcinogenic response in mammary gland</u> . At 23 mg/kg/day (at 2 years) combined fibroadenomas and carcinomas stat sig <u>only</u> when adjusted for survival; decr latency
MRID 42204401 Doc. 010771, 010705	

Atrazine Technical
Chronic Toxicity (Continued)

Minimum for onco- genicity (when con- sidered with Acces 262714-262727) <u>Limited Histopath</u>	period for onset of tumors. <u>Doses:</u> 0, 70 or 400 ppm in the diet (0, 3.8 or 23 mg/kg/day) to female Sprague Dawley rats.
83-2(a) 2-Year Oncogenicity in Female Fischer 344 Rats Hazleton Washington Study HWA 483-279 November 8, 1991 Thakur, A.K. MRID 42146101,42547106 42743903 Doc. 010422, 010705 Supplementary for oncogenicity <u>Limited Histopath</u>	<u>Females (only)</u> NOEL = 3.5 mg/kg/day LOEL = 10 mg/kg/day based on decr body weight gain. Only pituitary gland, uterus, ovaries and mammary gland exam. Negative for carcinogenicity. No decr latency period for onset of tumors. <u>Doses:</u> 0, 10, 70, 200 or 400 ppm in the diet (0, 0.5, 3.5, 10 or 20 mg/kg/day) to female Fischer 344 rats. Interim sacrifices at 1, 3, 9, 13, 15 and 18 months.
83-2(a) 2-Year Oncogenicity in Female Sprague Dawley Rats Hazleton Washington Study HWA 483-278 October 17, 1991 Thakur, A.K. MRID 42085001,42547107 42743902 Doc. (none--see EPA memo of 1/24/92) Not classified <u>Limited Histopath</u>	<u>Author's Conclusions--Not Reviewed by EPA</u> <u>Females (only)</u> NOEL = 3.5 mg/kg/day LOEL = 20 mg/kg/day based on decr body weight gain; incr mortality. Only pituitary gland, uterus, ovaries and mammary gland exam. <u>Positive carcinogenic response in mammary gland.</u> At 20 mg/kg/day, (at 2 years), no incr incidence of mammary or pituitary tumors, but time to tumor (latency period) was decreased for mammary gland and pituitary gland tumors. <u>Doses:</u> 0, 70 or 400 ppm in the diet (0, 3.5 or 20 mg/kg/day) to female Sprague Dawley rats. Interim sacrifices at 1, 3, 9, 12, 15 and 18 months.

Atrazine Technical

Chronic Toxicity (Continued)

83-2(b) 91-Week Oncogenicity
in CD-1 Mice
Ciba-Geigy Corp.
Study 842120
October 30, 1987
Hazelette & Green

MRID 40431302, 40629301
Doc. 006718, 006765

Males

NOEL = 38.4 mg/kg/day
LOEL = 194 mg/kg/day
based on decr body weight gain.
At 386 mg/kg/day, also decr food
consumption; incr cardiac thrombi;
decr RBC, Hg, Ht.
Negative for carcinogenicity.

Guideline for
Oncogenicity

Females

NOEL = 47.9 mg/kg/day
LOEL = 247 mg/kg/day
based on decr body weight gain;
incr cardiac thrombi.
At 483 mg/kg/day, also incr
mortality, decr food consumption;
decr RBC, Hg, Ht; decr brain &
kidney weights; decr % neutrophils
& lymphocytes.
Negative for carcinogenicity.

Doses: 0, 10, 300, 1500 or 3000
ppm in the diet (0, 1.4, 38.4, 194
or 386 mg/kg/day in males; 0, 1.6,
47.9, 247 or 483 mg/kg/day in
females) to CD-1 mice.

Atrazine Technical

Developmental and Reproductive Toxicity

Guide- line	Study Ident & Class	Results
83-3(a)	Developmental Toxicity in Rats (Oral) Ciba-Geigy Corp. Study 882049 February 23, 1989 Giknis, M.L.	<u>Maternal Toxicity</u> NOEL = 25 mg/kg/day LOEL = 100 mg/kg/day based on decr body weight gain, decr food consumption.
	MRID 41065201, 42089903 Doc. 008493 Minimum (DER docu- menting purity of TM and upgrading study still needs to be written)	<u>Developmental Toxicity</u> NOEL = 25 mg/kg/day LOEL = 100 mg/kg/day based on incr incid of delayed ossification of skull bones. <u>Doses:</u> 0, 5, 25 or 100 mg/kg/day by oral gavage to pregnant Sprague Dawley rats on days 6-15.
83-3(a)	Developmental Toxicity in Rats (Oral) Ciba-Geigy Corp. Study 60-84 September 18, 1984 Infurna, R.N.	<u>Maternal Toxicity</u> NOEL = 10 mg/kg/day LOEL = 70 mg/kg/day based on decr body weight gain, decr food consumption. At 700 mg/kg/day, high mortality.
	MRID 00143008, 40566302 Doc. 006131, 006761 Minimum	<u>Developmental Toxicity</u> NOEL = 10 mg/kg/day LOEL = 70 mg/kg/day based on incr incid of skeletal variations indicating delayed ossification. <u>Doses:</u> 0, 10, 70 or 700 mg/kg/day by oral gavage to pregnant Sprague Dawley rats on days 6-15.

Atrazine Technical

Developmental and Reproductive Toxicity (Continued)

- 83-3(b) Developmental Toxicity Maternal Toxicity
in Rabbits (Oral) NOEL = 5 mg/kg/day
Ciba-Geigy Corp. LOEL = 75 mg/kg/day
Study 68-84 based on decr body weight gain,
September 18, 1984 low food efficiency, incr in
Arthur, A.T. little, none and/or soft stools,
blood on vulva/in cage.
MRID 00143006, 40566301
Doc. 006131, 006761, Developmental Toxicity
009652 NOEL = 5 mg/kg/day
LOEL = 75 mg/kg/day
Minimum based on incr resorptions, decr
live fetuses, decr fetal weights.
Doses: 0, 1, 5 or 75 mg/kg/day
by oral gavage to pregnant New
Zealand rabbits on days 7-19.
- 83-4 2-Gen Reproduction Systemic Toxicity (Adult Rats)
Study in Rats NOEL = 2.5 mg/kg/day
Ciba-Geigy Corp. LOEL = 25 mg/kg/day
Study 852063 based on decr body weight gain,
November 17, 1987 decr food consumption, possible
Mainiero, J. et al. incr relative testes weights in
males.
MRID 40431303, 41986801
Doc. 006718 Reproductive Toxicity
See also TB memo NOEL = 2.5 mg/kg/day
(12/23/91) LOEL = 25 mg/kg/day
Minimum based on decr body weight of pups
of the second generation on post-
natal days 7 and 14.
This study was con-
sidered and then re-
jected by the RfD PRC
as the basis for the
RfD (in 1992). Doses: 0, 10, 50 or 500 ppm in the
diet (0, 0.5, 2.5 or 25 mg/kg/day)
to CD VAF/PLUS rats.

Hydroxyatrazine (G-34048) Technical
Subchronic/Chronic/Developmental Toxicity

Guide- line	Study Ident & Class	Results
82-1(a)	90-Day Feeding in Sprague Dawley Rats <u>Test Mat: Hydroxy- atrazine (G-34048)</u> Ciba-Geigy Corp. Study 882146 October 25, 1989 Rudzki, M.W. et al. MRID 41293501 Doc. 009647 Minimum	<u>Males</u> NOEL = 6.30 mg/kg/day LOEL = 18.9 mg/kg/day based on gross and histopath effects in kidney. At 37.5 mg/kg/day, also decr body weight gains; considerable damage to kidneys with secondary effects in extrarenal tissues; decr RBC, Ht and Hg; incr spleen weights, incr ultimobronchial bodies in thyroids. <u>Females</u> NOEL = 7.35 mg/kg/day LOEL = 22.7 mg/kg/day based on gross and histopath effects in kidney. At 45.6 mg/kg/day, essentially same as for males at 37.5 mg/kg/day. <u>Doses:</u> 0, 10, 100, 300 or 600 ppm in the diet. (0, 0.64, 6.30, 18.9 or 37.5 mg/kg/day in males; 0, 0.75, 7.35, 22.7 or 45.6 mg/kg/day in females) to Sprague Dawley rats.
82-1(b)	90-Day Feeding in Dogs <u>Test Mat: Hydroxy- atrazine (G-34048)</u> Ciba Geigy Corp. Study 892076 March 20, 1990 Chau, R.V. et al. MRID 41547901 Doc. none Not classified	<u>Author's Conclusions--Not Reviewed by EPA</u> <u>Males</u> NOEL = 5.8 mg/kg/day LOEL = 59.6 mg/kg/day based on gross and histopath effects in kidneys indicative of tubular and interstitial chronic nephropathy and intratubular cry- stals, secondary effects in extra- renal tissues. <u>Females</u> NOEL = 6.2 mg/kg/day LOEL = 63.9 mg/kg/day

Hydroxyatrazine (G-34048) Technical

Subchronic/Chronic/Developmental Toxicity (Continued)

based on same effects as for males at 59.6 mg/kg/day.

At 222.1 mg/kg/day, also emaciation (1 dog), sl decr body weight gain, sl decr food consumption.

Doses: 0, 15, 150, 1500 or 6000 ppm in the diet (0, 0.6, 5.8, 59.6 or 247.7 mg/kg/day in males; 0, 0.6, 6.2, 63.9 or 222.1 mg/kg/day in females) to Beagle dogs.

83-1(a) 2-Year Combined
83-2(a) Feeding/Oncogenicity
in Sprague Dawley Rats
Test Mat: Hydroxy-
atrazine (G-34048)
Ciba-Geigy Corp.
Study F-00125
January 27, 1995
Chow and Hart

MRID 42662901, 43314301
43532001
Doc. 011603, 011709
010158

Guideline for chronic
feeding and for
oncogenicity

Males

NOEL = 0.96 mg/kg/day

LOEL = 7.75 mg/kg/day

based on gross and histopath effects in kidney.

At 17.4 mg/kg/day, greatly decr body weights; severe renal damage leading to renal failure; secondary effects in extrarenal tissues; excessive mortality due to renal failure (survivors sac at 18 months).

Negative for carcinogenicity.

Females

NOEL = 1.17 mg/kg/day

LOEL = 9.53 mg/kg/day

based on gross and histopath effects in kidney.

At 22.3 mg/kg/day, same as for males at 17.4 mg/kg/day.

Negative for carcinogenicity.

Doses: 0, 10, 25, 200 or 400 ppm in the diet (0, 0.39, 0.96, 7.75 or 17.4 mg/kg/day in males; 0, 0.48, 1.17, 9.53 or 22.3 mg/kg/day in females) to Sprague Dawley rats.

Hydroxyatrazine (G-34048) Technical

Subchronic/Chronic/Developmental Toxicity (Continued)

83-3(a)	<u>Developmental Toxicity</u>	<u>Maternal Toxicity</u>
	in Rats (Oral)	NOEL = 25 mg/kg/day
	<u>Test Mat: Hydroxy-</u>	LOEL = 125 mg/kg/day
	<u>atrazine (G-34048)</u>	based on decr food consumption.
	Ciba-Geigy Corp.	
	Study 872202	<u>Developmental Toxicity</u>
	February 14, 1989	NOEL = 25 mg/kg/day
	Giknis, M.L.	LOEL = 125 mg/kg/day
	MRID 41065202, 42873702	based on decr fetal body weights,
	Doc. 008493, 010706	incomplete ossification of skull
		bones.
	Minimum	<u>Doses:</u> 0, 5, 25 or 125 mg/kg/day
		by oral gavage to pregnant
		Sprague Dawley rats on days 6-15.

Diaminochlorotriazine (DACT) (G-28273) Technical
Subchronic/Chronic/Developmental Toxicity

Guide- line	Study Ident & Class	Results
82-1(a)	90-Day Feeding in Sprague Dawley Rats <u>Test Mat: Diamino- chlorotriazine (DACT)</u> <u>(G-28273)</u> Ciba Geigy Corp. Study F-00006 November 5, 1991 Pettersen et al. MRID 43013207 Doc. none Guideline	<u>ACCORDING TO DRAFT DER BY ORNL</u> <u>Males</u> NOEL = 16.7 mg/kg/day LOEL = 34.1 mg/kg/day based on decr body weight gains. <u>Females</u> NOEL = 0.7 mg/kg/day LOEL = 7.6 mg/kg/day based on estrous cycle effects (incl lengthening of cycle and/or incr incid of rats with persistent estrus and/or diestrus). At 19.7 mg/kg/day, also decr body weight gain. <u>Doses:</u> 0, 10, 100, 250 or 500 ppm in the diet (0, 0.7, 6.7, 16.7 or 34.1 mg/kg/day in males; 0, 0.7, 7.6, 19.7 or 40.2 mg/kg/day in females) to Sprague Dawley rats.
83-1(b)	13/52-Week Chronic Feeding in Dogs <u>Test Mat: Diamino- chlorotriazine (DACT)</u> Ciba-Geigy Corp. Study 872151 January 17, 1990 Thompson, S.S. et al. MRID 41392401 Doc. 009497 Minimum	<u>Males</u> NOEL = 3.61 mg/kg/day LOEL = 24.1 mg/kg/day based on death (attributed to im- paired heart function), tremors, decr body weight gain, ascites, cardiac lesions (thickened valves, thrombosis, myocarditis, necrosis, etc.), secondary effects in liver, thymus, bone marrow and other organs. <u>Females</u> NOEL = 0.195 mg/kg/day LOEL = 3.43 mg/kg/day (threshold) based on tremors. At 32.7 mg/kg/day, same effects as males at HDT.

Diaminochlorotriazine (DACT) (G-28273) Technical
Subchronic/Chronic/Developmental Toxicity (Continued)

Doses: 0, 5, 100 or 1500/750 ppm
in the diet (0, 0.187, 3.61 or
24.1 mg/kg/day in males; 0, 0.195,
3.43 or 32.7 mg/kg/day in females)
to beagle dogs.

83-3(a) Developmental Toxicity
in Rats (Oral)

Test Mat: Diamino-
chlorotriazine (DACT)

Ciba-Geigy Corp.

Study 872177

August 15, 1989

Hummel, H. et al.

MRID 41392402, 42165502

Doc. 009497

Minimum

Maternal Toxicity

NOEL = 25 mg/kg/day

LOEL = 75 mg/kg/day

based on decr body weight gain,
decr food consumption.

Developmental Toxicity

NOEL = 2.5 mg/kg/day

LOEL = 25 mg/kg/day

based on incomplete ossification
of bones, possibly incr incid of
shortened or absent renal papilla.
At 75 mg/kg/day, also decr fetal
weights.

At 150 mg/kg/day, also incr re-
sorptions & postimplant loss.

Doses: 0, 2.5, 25, 75 or 150
mg/kg/day by oral gavage to
pregnant Sprague Dawley rats on
days 6-15.

G-28279 Technical

Subchronic/Chronic/Developmental Toxicity

Guide- line	Study Ident & Class	Results
82-1(a)	90-Day Feeding in Tif:RAIf(SPF) Rats <u>Test Mat: G-28279</u> Ciba Geigy (Switzer) Study 901261 May 8, 1992 Schneider, M. MRID 43013205 Doc. none Guideline	<u>ACCORDING TO DRAFT DER BY ORNL</u> <u>Males</u> NOEL = 3.2 mg/kg/day LOEL = 34.9 mg/kg/day based on decr body weight gains. At 34.9 mg/kg/day, also fatty changes in adrenal cortex, and hypertrophy in thyroid follicles. <u>Females</u> NOEL = 3.3 mg/kg/day LOEL = 37.5 mg/kg/day based on decr body weight gains. At 37.5 mg/kg/day, also incr liver weight and extramedullary hematopoiesis in liver. <u>Doses:</u> 0, 10, 50 or 500 ppm in the diet (0, 0.60, 3.2 or 34.9 mg/kg/day in males; 0, 0.64, 3.3 or 37.5 mg/kg/day in females) to Tif:RAIf(SPF) rats.
82-1(b)	90-Day Feeding in Dogs <u>Test Mat: G-28279</u> Ciba Geigy Corp. Study 912021 April 22, 1992 Thompson, S.S. et al. MRID 43013203 Doc. none Minimum	<u>ACCORDING TO DRAFT DER BY ORNL</u> <u>Males</u> NOEL = 3.8 mg/kg/day LOEL = 18.9 mg/kg/day based on possibly decr heart, testes and prostate gland weights. At 33.4 mg/kg/day, also decr body weight gain, decr food consump- tion, negative food efficiency (inanition). <u>Females</u> NOEL = 3.8 mg/kg/day LOEL = 18.0 mg/kg/day based on decr body weight gains, decr food consumption, negative food efficiency (inanition). <u>Doses:</u> 0, 15, 100, 500 or 1000 ppm in the diet (0, 0.6, 3.8, 18.9 or

G-28279 Technical

Subchronic/Chronic/Developmental Toxicity (Continued)

33.4 mg/kg/day in males; 0, 0.6, 3.8, 18.0 or 33.3 mg/kg/day in females) to Beagle dogs.

83-3(a) Developmental Toxicity ACCORDING TO DRAFT DER BY CLEMENT
in Rats (Oral)

Test Mat: G-28279

Ciba Geigy (Switzer)

Study 901262

June 1, 1992

Marty, J.H.

Maternal Toxicity

NOEL = 5 mg/kg/day

LOEL = 25 mg/kg/day

based on decr body weight gain,
decr food consumption.

MRID 43013208

Doc. none

Guideline

Developmental Toxicity

NOEL = 5 mg/kg/day

LOEL = 25 mg/kg/day

based on effects on skeletal
development (fused sternebrae).
At 100 mg/kg/day, also poor os-
sification of sternebrae and
digits.

Doses: 0, 5, 25 or 100 mg/kg/day
by oral gavage to pregnant
Tif:RAI rats on days 6-15.

G-30033 Technical

Subchronic/Chronic/Developmental Toxicity

Guide- line	Study Ident & Class	Results
82-1(a)	90-Day Feeding in Tif:RAIf(SPF) Rats <u>Test Mat: G-30033</u> Ciba Geigy (Switzer) Study 901264 October 22, 1991 Gerspach, R. MRID 43013206 Doc. none Supplementary (upgradable)	<u>ACCORDING TO DRAFT DER BY ORNL</u> <u>Males</u> NOEL = 36.3 mg/kg/day (HDT) No biologically significant effects. <u>Females</u> NOEL = 39.4 mg/kg/day (HDT) No biologically significant effects. <u>Doses:</u> 0, 10, 50 or 500 ppm in the diet (0, 0.71, 3.5 or 36.3 mg/kg/day in males; 0, 0.75, 3.7 or 39.4 mg/kg/day in females) to Tif:RAIf(SPF) rats.
82-1(b)	90-Day Feeding in Dogs <u>Test Mat: G-30033</u> Ciba Geigy Corp. Study 902187 April 16, 1992 Rudzki, M.N. et al. MRID 43013204 Doc. none Minimum	<u>ACCORDING TO DRAFT DER BY ORNL</u> <u>Males</u> NOEL = 3.71 mg/kg/day LOEL = 28.85 mg/kg/day based on decr body weight gains (attrib to inanition due to food palatability); renal tubular hyperplasia/basophilia; possibly decr heart weights, atrial fibrillation, and other heart damage; possible anemia. <u>Females</u> NOEL = 3.88 mg/kg/day LOEL = 32.18 mg/kg/day based on same effects as in males at 28.85 mg/kg/day. <u>Doses:</u> 0, 15, 100 or 1000 ppm in the diet (0, 0.56, 3.71, or 28.85 mg/kg/day in males; 0, 0.51, 3.88 or 32.18 mg/kg/day in females) to Beagle dogs.

G-30033 Technical

Subchronic/Chronic/Developmental Toxicity (Continued)

83-3(a) Developmental Toxicity ACCORDING TO DRAFT DER BY CLEMENT
in Rats (Oral)

Test Mat: G-30033
Ciba Geigy (Switzer)
Study 901265
June 1, 1992
Marty, J.H.

MRID 43013209
Doc. none

Guideline

Maternal Toxicity

NOEL = 5 mg/kg/day
LOEL = 25 mg/kg/day
based on decr body weight gain,
decr food consumption.

Developmental Toxicity

NOEL = 25 mg/kg/day
LOEL = 100 mg/kg/day
based on effects on skeletal
development (fused sternebrae),
poor ossification of digits.

Doses: 0, 5, 25 or 100 mg/kg/day
by oral gavage to pregnant
Tif:RAI rats on days 6-15.

TB596:ATRAZI06.066