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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BRB 6/6/96

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KB 6/9/96

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)
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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

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 Tisdel and Harris MRID 00163339 Doc. 006938 Supplementary	Males 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. Females 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. Doses: 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	Systemic Toxicity 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 protein & chloride (M only), incr cholesterol & triglycer (F only). Dermal Irritation NOEL = 100 mg/kg/day LOEL = 1000 mg/kg/day based on acanthosis, hyperkeratosis, focal inflammatiion, erythema, scaling of treated skin. Doses: 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) 83-2(a)	2-Year Combined Feeding/Oncogenicity in Sprague Dawley Rats American Biogenics Study 410-1102 April 29, 1986 Mayhew et al. MRID 00141874,00157875 00158930,40629302 Doc. 004453, 005940 Minimum for chronic feeding and for oncogenicity Study on which the RfD is presently based (as of June, 1996).	Males 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. Females 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. Positive carcinogenic response in mammary gland. 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. Doses: 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) 83-2(a)	1-Year Combined Feeding/Oncogenicity in Female Sprague Dawley Rats Ciba-Geigy Corp. Study F-00171 December 8, 1995 Pettersen and Turnier MRID 43598623,43934402 Doc. (under review) Not yet classified Limited Histopath	Author's Conclusions--Under Review by EPA (May, 1996) Females (only) 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. Only pituitary gland, mammary gland, ovaries, uterus, vagina, estrous cycle, and various hormone levels exam. Positive carcinogenic response in mammary gland. At 23.9 mg/kg/day (at 1

		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

		"thinness"; decr food consumption (weeks 1-13). Negative for carcinogenicity. Doses: 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) MRID (none) Doc. (none) Not classified	IARC's Conclusions*--Not Reviewed by EPA * IARC Monographs on the Eval of Carcinogenic Risks to Humans (1991) 53, p. 450. Males At 37.5 mg/kg/day, stat sig incr incid of mammary gland tumors (1/48, 1/51, 9/53, including 1 carcinoma). Females 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). Doses: 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. MRID 42204401 Doc. 010771, 010705	Females (only) 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). Positive carcinogenic response in mammary gland. At 23 mg/kg/day (at 2 years) combined fibroadenomas and carcinomas stat sig only when adjusted for survival; decr latency

	Minimum for oncogenicity (when considered with Acces 262714-262727) Limited Histopath	period for onset of tumors. Doses: 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 Limited Histopath	Females (only) 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. Doses: 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 Limited Histopath	Author's Conclusions--Not Reviewed by EPA Females (only) 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. Positive carcinogenic response in mammary gland. 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. Doses: 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.

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 Guideline for Oncogenicity	<u>Males</u> 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. <u>Females</u> 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. <u>Doses</u>: 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. MRID 41065201,42089903 Doc. 008493 Minimum (DER documenting purity of TM and upgrading study still needs to be written)	<u>Maternal Toxicity</u> NOEL = 25 mg/kg/day LOEL = 100 mg/kg/day based on decr body weight gain, decr food consumption. <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. MRID 00143008,40566302 Doc. 006131, 006761 Minimum	<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. <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.

83-3(b)	Developmental Toxicity in Rabbits (Oral) Ciba-Geigy Corp. Study 68-84 September 18, 1984 Arthur, A.T. MRID 00143006,40566301 Doc. 006131, 006761, 009652 Minimum	<u>Maternal Toxicity</u> NOEL = 5 mg/kg/day LOEL = 75 mg/kg/day based on decr body weight gain, low food efficiency, incr in little, none and/or soft stools, blood on vulva/in cage. <u>Developmental Toxicity</u> NOEL = 5 mg/kg/day LOEL = 75 mg/kg/day based on incr resorptions, decr live fetuses, decr fetal weights. <u>Doses</u>: 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 Study in Rats Ciba-Geigy Corp. Study 852063 November 17, 1987 Mainiero, J. et al. MRID 40431303,41986801 Doc. 006718 See also TB memo (12/23/91) Minimum <u>This study was considered and then rejected by the RfD PRC as the basis for the RfD (in 1992).</u>	<u>Systemic Toxicity (Adult Rats)</u> NOEL = 2.5 mg/kg/day LOEL = 25 mg/kg/day based on decr body weight gain, decr food consumption, possible incr relative testes weights in males. <u>Reproductive Toxicity</u> NOEL = 2.5 mg/kg/day LOEL = 25 mg/kg/day based on decr body weight of pups of the second generation on post-natal days 7 and 14. <u>Doses</u>: 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 Test Mat: Hydroxy-atrazine (G-34048) Ciba-Geigy Corp. Study 882146 October 25, 1989 Rudzki, M.W. et al. MRID 41293501 Doc. 009647 Minimum	Males 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. Females 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. Doses: 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 Test Mat: Hydroxy-atrazine (G-34048) Ciba Geigy Corp. Study 892076 March 20, 1990 Chau, R.V. et al. MRID 41547901 Doc. none Not classified	Author's Conclusions--Not Reviewed by EPA Males 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 crystals, secondary effects in extrarenal tissues. Females NOEL = 6.2 mg/kg/day LOEL = 63.9 mg/kg/day

		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) 83-2(a)	2-Year Combined 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)	Developmental Toxicity in Rats (Oral) Test Mat: Hydroxy-atrazine (G-34048) Ciba-Geigy Corp. Study 872202 February 14, 1989 Giknis, M.L. MRID 41065202,42873702 Doc. 008493, 010706 Minimum	Maternal Toxicity NOEL = 25 mg/kg/day LOEL = 125 mg/kg/day based on decr food consumption. Developmental Toxicity NOEL = 25 mg/kg/day LOEL = 125 mg/kg/day based on decr fetal body weights, incomplete ossification of skull bones. Doses: 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 Test Mat: Diamino-chlorotriazine (DACT) (G-28273) Ciba Geigy Corp. Study F-00006 November 5, 1991 Pettersen et al. MRID 43013207 Doc. none Guideline	ACCORDING TO DRAFT DER BY ORNL Males NOEL = 16.7 mg/kg/day LOEL = 34.1 mg/kg/day based on decr body weight gains. Females 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. Doses: 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 Test Mat: Diamino-chlorotriazine (DACT) Ciba-Geigy Corp. Study 872151 January 17, 1990 Thompson, S.S. et al. MRID 41392401 Doc. 009497 Minimum	Males NOEL = 3.61 mg/kg/day LOEL = 24.1 mg/kg/day based on death (attributed to impaired 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. Females 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.

		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 Test Mat: G-28279 Ciba Geigy (Switzer) Study 901261 May 8, 1992 Schneider, M. MRID 43013205 Doc. none Guideline	ACCORDING TO DRAFT DER BY ORNL Males 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. Females 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. Doses: 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 Test Mat: G-28279 Ciba Geigy Corp. Study 912021 April 22, 1992 Thompson, S.S. et al. MRID 43013203 Doc. none Minimum	ACCORDING TO DRAFT DER BY ORNL Males 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 consumption, negative food efficiency (inanition). Females 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). Doses: 0, 15, 100, 500 or 1000 ppm in the diet (0, 0.6, 3.8, 18.9 or

		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 in Rats (Oral) Test Mat: G-28279 Ciba Geigy (Switzer) Study 901262 June 1, 1992 Marty, J.H. MRID 43013208 Doc. none Guideline	ACCORDING TO DRAFT DER BY CLEMENT Maternal Toxicity NOEL = 5 mg/kg/day LOEL = 25 mg/kg/day based on decr body weight gain, decr food consumption. 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 ossification 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 Test Mat: G-30033 Ciba Geigy (Switzer) Study 901264 October 22, 1991 Gerspach, R. MRID 43013206 Doc. none Supplementary (upgradable)	ACCORDING TO DRAFT DER BY ORNL Males NOEL = 36.3 mg/kg/day (HDT) No biologically significant effects. Females NOEL = 39.4 mg/kg/day (HDT) No biologically significant effects. Doses: 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 Test Mat: G-30033 Ciba Geigy Corp. Study 902187 April 16, 1992 Rudzki, M.N. et al. MRID 43013204 Doc. none Minimum	ACCORDING TO DRAFT DER BY ORNL Males 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. Females 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. Doses: 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.

83-3(a)	Developmental Toxicity in Rats (Oral) Test Mat: G-30033 Ciba Geigy (Switzer) Study 901265 June 1, 1992 Marty, J.H. MRID 43013209 Doc. none Guideline	ACCORDING TO DRAFT DER BY CLEMENT 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.