## Appendix J HED Effects Table

| Guideline/Study Type | MRID/Report # /Date/Study Classification | Results |
|---|---|---|
| 81-1<br><br>Acute Oral Toxicity in Rats | MRID 00141662<br>Report # 84-063A<br>Date: 7/19/84<br><br>Acceptable | $LD_{50}$: 1.6 g/kg (males)<br>$LD_{50}$: 2.29 g/kg (females)<br><br>TOXICITY CATEGORY: III |
| 81-2<br><br>Acute Dermal Toxicity in Rabbits | MRID 00141663<br>Report # 84R-134A<br>Date: 7/30/84<br><br>Acceptable | $LD_{50}$: >5000 mg/kg<br><br>TOXICITY CATEGORY: III |
| 81-3<br><br>Acute Inhalation Toxicity in Rats | MRID 40357101<br>Report # 87R-028<br>Date: 8/31/87<br><br>Acceptable | $LC_{50}$: >5.1 mg/L<br>(Four hour exposure)<br><br>TOXICITY CATEGORY: IV |
| 81-4<br><br>Primary Eye Irritation in Rabbits | MRID 00141663<br>Report # 84R134A<br>Date: 8/3/84<br><br>Acceptable | Primary Irritation Score: Not given in DER.<br><br>TOXICITY CATEGORY: I<br>Severe eye irritant |
| 81-5<br><br>Primary Dermal Irritation in Rabbits | MRID 00141663<br>Report # 84R-134A<br>Date: 8/3/84<br><br>Acceptable | Primary Irritation Score: Not given in DER<br><br>TOXICITY CATEGORY: IV<br>Non-irritating to the skin under conditions of test. |
| 81-6<br><br>Dermal Sensitization in Guinea Pigs | MRID 40357102<br>Report # 87R-035<br>Date: 6/25/87<br><br>Acceptable | Buehler method. 12 pigs, 10 induction doses of 0.4 ml of 50% w/w formulation in 80% ethanol. 50% w/w formulation in acetone used at challenge + rechallenge. Minimal erythema at 24 & 48 hrs. Positive sensitizing reaction. |
| 82-1 (a)<br><br>Subchronic Feeding in Rats (13 weeks) | MRID 145048<br>Report # 83R-068<br>Date: 8/7/84<br><br>Core Grade: Minimum | NOEL: 1000 ppm<br>LOEL: 3000 ppm<br><br>Effects: increased liver, kidney wts.; hypertrophy, necrosis in liver; pigmentation in convoluted |

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| | | kidney tubules; vacuolated adrenal cortex. |
| 82-1 (b)<br><br>Subchronic Feeding in Dogs (13 Weeks) | MRID 00141670<br>Report # 83R-204<br>Date: 8/7/84<br><br>Core Grade: Minimum | NOEL: 10 ppm<br>LOEL: 200 ppm<br><br>Effects: Technical myclobutanil, (81.1%) tested at: 0, 10, 200, 800 or 1600 ppm (0, 0.34, 7.26, 29.13 or 56.80 mg/kg/day (males) and 0, 0.42, 7.88, 32.43 or 57.97 mg/kg/day (females)). At 200 ppm and above, hepatocellular centrilobular or midzonal hypertrophy was observed in males. At 800 ppm and above, the same effect was observed in females. In addition, increases in alkaline phosphatase, in absolute liver weights in both sexes and in relative liver weights in males were observed. At 1600 ppm, all the previous effects plus increases in relative liver weights in females, a suggestion of mild red cell destruction or mild anemia, and decreases in body weight and food consumption (possibly related to palatability) were observed. |
| 83-1<br><br>Chronic feeding study in dogs | MRID 00165248<br>Report # 84R-078<br>Date: 10/15/86<br><br>Core Grade: Minimum | NOEL: 100 ppm<br>LOEL: 400 ppm<br><br>Effects: 91.4% material fed in the diet to 6 dogs/group/dose at levels of 0, 10, 100, 400 or 1600 ppm for one year. LEL: 14.28 mg/kg/day; the NOEL: 3.09 |

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| | | mg/kg/day based on hepatocellular hypertrophy, increases in liver weights, "ballooned" hepatocytes and increases in alkaline phosphatase, SGPT and GGT. In addition, there were some possible slight hematological effects. Full histopathology examinations not submitted for mid- and low dose level groups. |
| 83-2 (a)<br><br>Oncogenicity study in mice | MRID 00164990<br>Report # 84R-023<br>Date: 10/17/86<br><br>Core Grade: Minimum when considered with MRID 428091-02 | NOEL: 100 ppm (Systemic)<br>LOEL: 500 ppm (Systemic)<br><br>Effects: 90.4% test material given to male & female Crl:CD®-1(ICR)BR mice in diet for 24 months at 0, 20, 100 or 500 ppm (0, 2.7, 13.7 or 70.2 mg/kg/day _; 0, 3.2, 16.5 or 85.2 mg/kg/day). LEL based on ↑ MFO (_+_); ↑ SGPT (_) & ↑ absolute & relative liver wts (_+_); ↑ incidences and severity of centrilobular hepatocytic hypertrophy, Kupffer cell pigmentation, periportal punctate vacuolation & individual hepatocellular necrosis (_); & ↑ incidences of focal hepatocellular alterations and multifocal hepatocellular vacuolation (_+_). Not tested at high enough dose levels in females. MRID No. 428091-02 tested at sufficiently high dose levels (2000 ppm (393.5 mg/kg/day)), no oncogenic effects observed. The two studies together satisfy the regulatory requirement for an |

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| | | oncogenicity study in the mouse. |
| 83-2 (a)<br><br>Oncogenicity study in mice | MRID 42809102<br>Report # 89R-261<br>Date: 3/17/93<br><br>Core Grade: Minimum when considered with MRID 00164990 | NOEL: Not established<br>LOEL: 2000 ppm (393.5 mg/kg/day)<br><br><u>Effects</u>: Technical (92.9%) administered to female Crl:CD®-1(ICR)BR mice at 0 or 2000 ppm (393.5 mg/kg/day) in diet. Decreases in body wt & body wt gain; increases in liver wts; hepatocellular hypertrophy; hepatocellular vacuolation; necrosis of single hypertrophied hepatocytes; yellow-brown pigment in the Kupffer cells and cytoplasmic eosinophilia and hypertrophy of the cells of the zona fasciculata area of the adrenal cortex. Not oncogenic under the conditions of the study. Study is only 18 months, however, the two studies together satisfy the regulatory requirement for an oncogenicity study in the mouse. |
| 83-2 (b)<br><br>Oncogenicity study in rats | MRID 42809101<br>Report # HWA 417-471, RH-89RC-260<br>Date: 2/12/93<br><br>Core Grade: Guideline when taken in conjunction with MRID 00165247 | NOEL: Not established<br>LOEL: 2500 ppm (only dose tested)<br><br>Effects: (92.9%) administered to _+_ Sprague-Dawley Crl:CD®BR VAF/Plus® rats at 0 or 2500 ppm (125 mg/kg/day) in the diet. Testicular atrophy and decreases in testes weights; increases in the incidences of centrilobular to midzonal |

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| | | hepatocellular enlargement and vacuolization in the liver of both sexes; increases in bilateral aspermatogenesis in the testes; increases in the incidence of hypospermia and cellular debris in the epididymides; and increased incidence of arteritis/periarteritis in the testes). No oncogenic effects observed. Satisfies regulatory requirement when taken with MRID 00165247. |
| 83-3<br><br>Teratology Study in Rabbits | MRID 00164971<br>Report # 83R-217<br>Date: 11/15/84<br><br>Core Grade Minimum | Maternal NOEL: 60 mg/kg/day<br>Maternal LOEL: 200 mg/kg/day<br><br>Effects: technical 90.4% administered to New Zealand White rabbits 0 (water control), 0 (Hi-Sil control), 20.0, 60.0 or 200.0 mg/kg/day a.i. by oral gavage (5 ml/kg b.w.) on days 7 - 19 of gestation. Reduced body weight and body weight gain during the dosing period, clinical signs of toxicity and possibly abortions.<br><br>Developmental NOEL: 60 mg/kg/day<br>Developmental LOEL: 200 mg/kg/day<br><br>Effects: Increases in number of resorptions, decreases in litter size and a decrease in the viability index. |
| 83-3<br><br>Teratology Study in Rats | MRID 00141672<br>Report # 83R-024<br>Date: 6/22/84 | Maternal NOEL: 93.8 mg/kg/day<br>Maternal LOEL: 312.6 |

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| | Core Grade Minimum | mg/kg/day<br><br>Effects: Technical (84.5 %) administered to Sprague-Dawley [Crl:CD-(SD)BR] rats at 0, 31.26, 93.77, 312.58 or 468.87 mg/kg/day by oral gavage from gestation days 6 -15, inclusive. Rough hair coat and salivation at 312.6 and salivation, alopecia, desquamation and red exudate around mouth at 468.87 mg/kg/day.<br><br>Developmental NOEL: 93.8 mg/kg/day Developmental LOEL: 312.6 mg/kg/day<br><br>Effects: Increased incidences of 14th rudimentary and 7th cervical ribs at 312.6 and 468.9 mg/kg/day. |
| 83-4<br><br>Multigeneration Reproduction Toxicity in Rats | MRID 00143766 and 00149581<br>Report # 84R-117<br>Date: 8/21/85<br><br>Core Grade Guideline | Systemic NOEL: 50 ppm (2.5 mg/kg/day)<br>Systemic LOEL: 200 ppm (10 mg/kg/day)<br><br>Effects: Technical (84.5% pure) administered to male and female CRL:CD(SD)BR rats at 0, 50, 200 or 1000 ppm in diet (0, 2.5, 10 or 50 mg/kg/day). ↑ liver weights and hepatocellular hypertrophy.<br><br>Reproductive NOEL: 200 ppm (10 mg/kg/day)<br>Reproductive LOEL: 1000 ppm (50 mg/kg/day)<br><br>Effects: Increased incidence in the number of stillborns |

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| | | and atrophy of the testes, epididymides and prostate.<br><br>Developmental NOEL: 200 ppm (10 mg/kg/day)<br>Developmental LOEL: 1000 ppm (50 mg/kg/day)<br><br>Effects: Decrease in pup body weight gain during lactation. |
| 83-5<br><br>Chronic Feeding/ Oncogenicity study in rats | MRID 00165247<br>Report # 85RC-61<br>Date: 10/24/86<br><br>Core Grade: Guideline when taken in conjunction with MRID 428091-01 | NOEL: 2.49 mg/kg/day<br>LOEL: 9.84 mg/kg/day<br><br>Effects: Technical (90.4% and 91.4% pure) administered to _+_ Sprague-Dawley rats in diet for 24 months at 25/35/50, 100/140/200 & 400/560/800 ppm (2 weeks/2 weeks/to termination; 0, 2.49, 9.84 or 39.21 mg/kg/day (_); 0, 3.23, 12.86 or 52.34 mg/kg/day (_). ↓ testes wts & ↑ in testicular atrophy. Not tested at high enough dose levels. MRID No. 428091-01 tested at sufficiently high dose levels (2500 ppm: 125 mg/kg/day), no oncogenic effects observed. Satisfies regulatory requirment when taken with MRID 428091-01. |
| 84-2 (a)<br><br>Gene Mutation Assay (Ames Test) | MRID 00141673<br>Report # 83R-0246<br>Date: 1/31/84<br><br>Acceptable | No appreciable increase in the reversion to histidine protrophy of 4 S. typhimurium strains at 75 to 7500 ug/plate with & without S-9 activation. |
| 84-2 (a)<br><br>Gene Mutation Assay | MRID 00141674<br>Report # 84R-046<br>Date: 5/29/84 | Negative with and without metabolic activation up to 175 ug/ml. |

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| Mammalian Cells | Acceptable | |
| 84-2 (b)<br><br>Structural Chromosomal Aberration Assay<br>In vivo cytogenetics | MRID 00141675<br>Report # 84R-0074<br>Date: 7/23/84<br><br>Acceptable | The level of 650 mg/kg did not cause a significant increase in chromosomal aberrations in bone marrow cells sampled over the entire mitotic cycle. |
| 84-2 (b)<br><br>Structural Chromosomal Aberration Assay In vitro cytogenetics | MRID 00164972<br>Report # 20990<br>Date: 4/85<br><br>Acceptable | Did not induce chromosomal aberrations with & without metabolic activation under the conditions of the study up to 200 ug/ml. |
| 84-2 (b)<br><br>Structural Chromosomal Aberration Assay<br>Dominant Lethal Test | MRID 00164974<br>Report # 86RC-0054<br>Date: 10/10/86<br><br>Acceptable | Did not induce dominant lethal mutations under conditions of study at dose levels up to 735 mg/kg. |
| 84-2 (c)<br><br>Other Genotoxicity Assays (Unscheduled DNA Synthesis) | MRID 00164973<br>Report # 86R-084 Date: 7/22/86<br><br>Acceptable | Did not induce an increase in unscheduled DNA synthesis up to toxic dose. 0.1-1000 ug/ml tested. |
| 85-1<br><br>Metabolism | MRID 00164975<br>Report # 83R-175<br>Date: 8/29/86<br><br>Acceptable | Rapidly absorbed and excreted. Completely eliminated by 96 hrs. Extensively metabolized prior to excretion. Metabolic patterns similar for both sexes. Disposition & metabolism after pulse administration is linear over dose range. |
| 85-1<br><br>Metabolism | MRID 00164976<br>Report # 83R-144<br>Date: 8/28/86<br><br>Acceptable | Completely and rapidly absorbed. Extensively metabolized and rapidly and essentially completely excreted. Elimination of label from plasma biphasic and evenly distrib. between urine and feces. No tissue accumulation after 96 hours. |

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| 85-1<br><br>Metabolism | MRID 00145682<br>Report # 310-84-16<br>Date: 6/22/84<br><br>Acceptable | At least 7 major metabolites recovered and identified. Highest amounts of radioactivity found in liver, kidneys, large and small intestines. No tissue accumulation. |