APPENDIX J HED Ziram Toxicity Profile

Table 2. Ziram Toxicology Profile		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Results**
870.3100 90-Day oral toxicity-rat	42450301 (1992) Acceptable/guideline 0, 100, 300, 1000 ppm M: 0, 7.4, 21.4, 67.8 mg/kg/day F: 0, 8.8, 24.2, 76.9 mg/kg/day	NOAEL = [M: 7.4, F: 8.8] mg/kg/day LOAEL = [M: 21.4, F: 24.2] mg/kg/day based on decreases in body weight, body weight gain, food consumption, and minimal histopathological changes in the female liver
870.3150 90-Day oral toxicity-dog	N/A (requirement fulfilled by chronic dog study)	N/A
870.3200 21/28-Day dermal toxicity-rabbit	41297001 (1989) Acceptable/guideline M&F: 0, 100, 300, 1000 mg/kg	NOAEL = [M: >1000, F: 300] mg/kg LOAEL = [F: 1000] mg/kg based on decreased body weight and food consumption and clinical chemistry suggestive of minimal hepatotoxicity. A LOAEL was not observed in males.
870.3250 90-Day dermal toxicity	NA	NA
870.3465 90-Day inhalation toxicity	NA	NA
870.3700a Prenatal developmental-rat	41908701 (1990) Acceptable/guideline F: 0, 1, 4, 16, 64 mg/kg/day	**Maternal** NOAEL = [4] mg/kg/day LOAEL = [16] mg/kg/day based on decreased body weights, reduced food consumption, salivation, and increased water intake. **Developmental** NOAEL = [4] mg/kg/day LOAEL = [16] mg/kg/day based diaphragmatic thinning
870.3700b Prenatal developmental-rabbit	00161316 (1986) Acceptable/guideline F: 0, 3, 7.5, 15 mg/kg/day	**Maternal** NOAEL = [3] mg/kg/day LOAEL = [7.5] mg/kg/day based on decreased body weight gain. **Developmental** NOAEL = [7.5] mg/kg/day LOAEL = [15] mg/kg/day based on increased incidence of resorptions and post-implantation loss.
870.3800 Reproduction and fertility effects-rat	43935801 (1996) Acceptable/guideline 0,72, 207, 540 ppm F_0 males: 0, 5.3, 14.8, 37.5 mg/kg/day F_0 females: 0, 6.1, 16.8, 42.8 mg/kg/day F_1 males: 0, 5.6, 16.7, 42.7 mg/kg/day F_1 females: 0, 6.3, 18.4, 47.5 mg/kg/day	**Parental/Systemic** NOAEL = [14.8] mg/kg/day LOAEL = [37.5] mg/kg/day based on reduced body weights, body weights gains, and food consumption in the F_0 and F_1 males and females. **Offspring** NOAEL = [16.8] mg/kg/day LOAEL = [42.8] mg/kg/day based on decreased body weights at birth in F_2 pups and during lactation in F_1 and F_2 pups.

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870.4100a Chronic toxicity-CD rat	43404201 (1994) Acceptable/guideline 0, 60, 180, 540 ppm M: 0, 2.5, 7.7, 23.7 mg/kg/day F: 0, 3.4, 10.2, 34.6 mg/kg/day	NOAEL = not established LOAEL = [M: 2.5, F: 3.4] mg/kg/day based on histopathological findings in various organs.
870.4100a Chronic toxicity- F344 rat	NTP (1983) Acceptable/guideline 0, 300, or 600 ppm M: 0, 11, or 22 mg/kg/day F: 0, 13,or 26 mg/kg/day	NOAEL = [M: 22, F: 26] mg/kg/day based on lack of effect. LOAEL = [M: >22, F: >26] mg/kg/day
870.4100a Chronic toxicity- F344 rat	45770201 (1983) Acceptable/guideline 0, 20, 200, or 2,000 ppm M: 0, 0.70, 6.9, or 74 mg/kg/day F: 0, 0.83, 8.5, or 91 mg/kg/day	NOAEL = [M: 0.70, F:0.83] mg/kg/day LOAEL = [M: 6.9, F: 8.5] mg/kg/day based on slight anemia in females, decreases in the absolute and relative weight of the crural muscle in both sexes, atrophy of the crural muscle in both sexes, increased mucosal cornification of the stomach in both sexes, follicular cell hypertrophy of the thyroid in females, and rhinitis of the nasal cavity in females.
870.4100b Chronic toxicity- dog	42823901 (1993) Acceptable/guideline 0, 50, 185, 700 ppm M: 0, 1.6, 6.6, 17.4 mg/kg/day F: 0, 1.9, 6.7, 20.6 mg/kg/day	NOAEL = [M: 1.6, F: 1.9] mg/kg/day LOAEL = [M: 6.6, F: 6.7] mg/kg/day based on decrease in body weight gain in the females and liver histopathology in males.
870.4200a Carcinogenicity- CD rat	Same as chronic toxicity-CD rat above (870.4100a).	**Evidence of carcinogenicity** based on increased incidence of benign hemangiomas in CD male rats at 23.7 mg/kg/day
870.4200a Carcinogenicity- F344 rat	Same as chronic toxicity-F344 rat above (870.4100a).	**Evidence of carcinogenicity** based on increased incidence of thyroid C-cell carcinoma in male rats at 22 mg/kg/day
870.4200a Carcinogenicity- F344 rat	Same as chronic toxicity-F344 rat above (870.4100a).	**Evidence of carcinogenicity** based on increased incidence of preputial gland adenomas in male rats at 74 mg/kg/day.
870.4200b Chronic/Carcinogenicity- CD-1 mouse	43373701 (1994) Acceptable/guideline 0, 29, 75, 225, 675 ppm M: 0, 3, 9, 27, 82 mg/kg/day F: 0, 4, 11, 33, 95 mg/kg/day	NOAEL = [M: 9, F: 11] mg/kg/day LOAEL = [M: 27, F: 33] mg/kg/day based on decreased absolute brain weight in both sexes and increased incidence of urinary bladder epithelial hyperplasia and decreased body weight gain in CD-1 males. **No evidence of carcinogenicity**

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870.4200b Chronic/Carcinogenicity- B6C3F1 mouse	NTP (1983) Acceptable/guideline 0, 600, or 1200 ppm M: 0, 122, or 196 mg/kg/day F: 0, 131, 0r 248 mg/kg/day	NOAEL = [M:196]mg/kg/day; not established for females; LOAEL = [M: >196, F: 131] mg/kg/day based on increased incidence of alvelolar epithelial hyperplasia in females **Evidence of carcinogenicity** based on increased incidence of alveolar/bronchiolar adenomas and of combined alveolar/bronchiolar adenomas or carcinomas in female B6C3F1 mice at ≥131 mg/kg./day
Gene Mutation 870.5265 Salmonella/ mammalian activation gene mutation assay	00147462 (1984) Acceptable/guideline 41642901 (1990) Acceptable/guideline Haworth, et al. (1983) Acceptable/guideline	The test article was positive for gene mutation induction in strain TA100 (±S9). The test article was mutagenic when tested above 50 µg/plate (+S9). The test article was positive in strains TA100 (±S9) and TA1535 (+S9)
Cytogenetics 870.5375 *in vitro* mammalian cytogenetics assay	41287802 (1989) Acceptable/guideline Gulati (1989) Acceptable/guideline	There was no evidence of structural chromosomal aberrations over background. The test article was positive for chromosomal aberrations (±S9).
870.5300 mammalian cell gene mutation assay	45806501(1999) Acceptable/guideline	No reproducible increase in the mutation frequency of mouse lymphoma cells was seen
870.5300 mammalian cell gene mutation assay	McGregor, et al. (1988) Acceptable/guideline	The test article was positive for gene mutation induction (-S9).
870.5395 mammalian erythrocyte micronucleus test	Proudock, R.L. and Taylor, K. (1992 Unacceptable - maximum tolerated dose not tested, dosing regime not justified, and non-standard procedures used.	The test article was negative in the peripheral blood of CD-1 Swiss mice fed levels of 25, 75, 225, or 675 ppm for 89 days.
Other Genotoxicity 870.5550, Unscheduled DNA synthesis	41287801 (1989) Acceptable/guideline	There was no evidence that unscheduled DNA synthesis was induced.
870.6200a Acute neurotoxicity screening battery	43362801 (1994) Acceptable/guideline M&F: 0, 15, 300, 600 mg/kg	NOAEL = not established LOAEL = [M&F: 15] mg/kg/day based on ataxia and slight impairment of gait in males.

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870.6200b Subchronic neurotoxicity screening battery	43413701 (1994) Acceptable/guideline 0, 72, 207, 540 ppm M: 0, 5, 14, 34 mg/kg/day F: 0, 6, 16, 40 mg/kg/day	**Systemic** NOAEL = [M: 14, F: 16] mg/kg/day LOAEL = [M: 34, F: 40] mg/kg/day based on decreased body weight and body weight gains. **Cholinesterase** NOAEL = [M: 14, F: 6] mg/kg/day LOAEL = [M: 34, F: 16] mg/kg/day based on brain cholinesterase inhibition in both sexes and brain neurotoxic esterase activity in the males.
870.6300 Developmental neurotoxicity	43935801 (1996) Unacceptable/guideline 0, 72, 207, 540 ppm Maternal gestation: 0, 5, 13, 32 mg/kg/day Maternal lactation: 0, 11, 30, 79 mg/kg/day	**Maternal** NOAEL = [13] mg/kg/day LOAEL = [32] mg/kg/day based on reduced body weights and/or body weights gains, and decreased food consumption during gestation and lactation. **Offspring** NOAEL = not established LOAEL = [5] mg/kg/day based on increased motor activity.
870.7485 Metabolism and pharmaco-kinetics-rat	42391001 (1992) Unacceptable/guideline M&F: 15, 352 mg/kg or 15 mg/kg/day	The test material was rapidly absorbed and excreted via the urine and expired air, and significant amounts were excreted in the feces. Small amounts were widely distributed in the body. Metabolites were not identified.
870.7600 Dermal penetration	Same as 21-day dermal rabbit (870.3200) and rabbit oral developmental (870.7600).	The test material was minimally absorbed.