Supplement to Document No.010278 and 011019 - DER for MRID No. 42570701: 2-Generation Reproduction Study in Rats. This supplement provides an Executive Summary to upgrade the

EPA Reviewer: Abdallah Khasawinah, Ph.D., Date _____
Reregistration Branch 4 (7509C)
EPA Secondary Reviewer: Sanjivani Diwan, Ph.D., Date _____
Reregistration Branch 4 (7509C)

DATA EVALUATION RECORD

STUDY TYPE: Reproduction Study - Rat; OPPTS 870.3800 [§83-4]

DP BARCODE: D262725 SUBMISSION CODE: S548748
P.C. CODE: 111901 TOX. CHEM. NO.: 497AB

TEST MATERIAL (PURITY): Imazalil technical (≥95.0%) (Deccozil™)

SYNONYMS: R23979; Fungaflor Technical; 1-[2-(2,4-dichlorophenyl)-2-(2-propenyloxy)ethyl]-1H-imidazole

CITATION: Dirkx, P.; Van Cauteren, H., 1992. 2-Generation Reproduction Study with 1 Litter Per Generation in Wistar Rats. Study number 2337. Dept. of Toxicology, Janssen Research Foundation, 2340 Beerse, Belgium. October 26, 1992. MRID 42570701. Unpublished.

SPONSOR: Janssen Pharmaceutica N.V., 2340 Beerse, Belgium

EXECUTIVE SUMMARY: In a 2-generation reproduction study (MRID 42570701), imazalil (≥95.0%) was administered in the diet to a non-inbred strain of 24 Wistar rats per sex at approximately 0, 5, 20 or 80 mg/kg/day for 60 days prior to mating, through mating and lactation (females only). The F1 generation was administered the same dietary concentrations for similar periods. Mating was approximately 1 male to 3 females in the second generation rather than 1 male to 1 female. Twenty four F1 females were mated at each level except for the high dose level where 14 females were mated only to produce the F2 generation. Only one litter per generation was produced.

**Parental toxicity**. Test material related toxicity was seen at the high dose level. A statistically significant increase in dystocia was seen in the P0 dams (3/24 in controls vs 6/24, $p \leq 0.05$) and F1 dams (1/24 in controls vs 8/14, $p \leq 0.05$) associated

with the end of the gestation. A red vaginal discharge (incidence frequency not reported in the DER) was seen in the P0 dams during lactation. Food wastage occurred at the high dose in the P0 females from week 2 prior to mating, during gestation and lactation and in F1 females during pregnancy and lactation which negates food efficiency calculations. Body weight and body weight gains were decreased (95% of controls) in P0 males. Body weight decreases occurred in P0 and F1 females during gestation (76-80% of controls, $p \leq 0.05$) and lactation (94% of controls, $p \leq 0.01$). Increased liver vacuolation occurred in P0 males (11/24) vs. 0/24) in controls, mean score 0.5, $p \leq 0.05$) and possibly in F1 males (1/7 vs. 0/20 in controls, mean score 0.14. $p \geq 0.05$). The parental toxicity **LOAEL** is 80 mg/kg/day based on body weight and body weight gain decreases and increased liver vacuolation in males in addition to the other toxic symptoms described above. The parental toxicity **NOAEL** is 20 mg/kg/day.

**Parental Reproductive Toxicity**. A treatment related effect on the length of gestation (significantly increased by approximately 1 day in both P0 and F1 females) was noted at the high dose. Based on the increased duration of gestation for the P0 and F1 females, the reproductive toxicity **LOAEL** is 80 mg/kg/day and the **NOAEL** is 20 mg/kg/day.

**Offspring Toxicity.** There was a statistically significant decreased litter size at birth from the dams producing the F1 and F2 litters(54% and 51% of control values for F1 and F2, respectively) at the high dose. The number of dead pups at birth were also statistically ($p \leq 0.05$ to $p \leq 0.0001$) increased at the high dose in both generations. A nominal trend (statistical analysis was not conducted for trend) for decreased implantation sites in both generations was observed. The decreased number of implantation sites was statistically significant ($p \leq 0.05$) in the F2 females at the high dose. Survival during lactation was significantly ($p \leq 0.05$ to $p \leq 0.0001$) reduced at all dose levels in the F1 pups and at the low dose and high dose levels in the F2 pups. Additional information provided by the registrant in response to several questions by the EPA reviewers of the study clarified the pup survival issue. A review of these responses (HED document no. 011019) considered the apparent decreased F1 pup survival at all dose levels as not real because there was a strong litter effect in the data and the registrant based the statistical analysis on the fetus. Additional statistical analysis on pup mortality by litter was significant only at the HDT. The offspring toxicity **LOAEL** is 80 mg/kg/day based on pup mortality from birth to day 4 and the **NOAEL** is 20 mg/kg/day.

This reproductive study in rats was initially classified



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**supplementary** (HED document no.010278) due to several questions by the reviewers regarding historical control data, environmental conditions, mating rational, additional data on F1 males, homogeneity and stability of the test material in the diet and data clarifications. The registrant's responses were found acceptable (HED document no.011019) and the study was upgraded to **acceptable** for a guideline (83-4) study for effects on reproduction in the rat.

COMPLIANCE: Signed and dated GLP, Quality Assurance provided.



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