



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

September 8, 2006

MEMORANDUM

Subject: Ethaboxam: Revised Human Health Risk Assessment for Requested Tolerances on Grapes and Processed Commodities.
PC Code: 090205
Petition No: 4E6863
DP Number: D332315

Regulatory Action: Tolerance without a U.S. Registration
Risk Assessment Type: Single Chemical Aggregate

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This document is a revision of the human health risk assessment for ethaboxam issued by HED on June 20, 2006 (M. Doherty, K. Bailey, DP No. 310098). The original assessment has been changed to remove several statements regarding the need for additional testing to elucidate potential endocrine effects from ethaboxam (p. 12 and P. 25). The intent of the original assessment was to indicate that because there are known endocrine effects associated with ethaboxam, additional testing may be requested in the future (in accordance with the Endocrine Disruption Screening Protocols). However, there are no specific studies being requested at this time because endocrine effects have been well-characterized in an acceptable 2-generation reproduction study with a clear NOAEL/LOAEL, and the chronic reference dose (cRfD) selected

for ethaboxam risk assessments is considered protective. To the extent that new or revised tests are developed in connection with the endocrine disruption screening program that can provide more information on endocrine effects, EPA will consider whether further testing of ethaboxam is appropriate. Because the toxicity database for ethaboxam is complete (i.e., there are no data gaps), there is no evidence of susceptibility, and all adverse effects have been well-characterized and are addressed by at least a safety factor of 100X, HED recommended the 10X FQPA safety factor be reduced to 1X. In addition to the revised statements regarding testing for endocrine disruption, this revised risk assessment deletes the need for submission of an analytical reference standard and completion of the Agency method validation on pages 4, 28 and 29; the analytical reference standard has been received, and a successful Agency method validation was completed.

As noted above, the only exposure pathway that is expected for ethaboxam is dietary exposure. To assess dietary exposure, HED has used the Dietary Exposure Evaluation Model with the Food Commodity Intake Database (DEEM-FCID) with highly health-protective assumptions regarding level and prevalence of ethaboxam residues in grapes and processed grape commodities. Risk estimates based on these assumptions are below HED's level of concern for all population subgroups, including those of infants and children.

HED has evaluated the available data and is recommending that a permanent tolerance of 6.0 ppm be established for residues of ethaboxam in/on grape pending resolution of the deficiencies, as noted in Section 10 of this document. HED further recommends that the CFR entry clearly states that there is no U.S. registration for ethaboxam on grapes at this time.

Guideline Number	Study Type Classification	MRID Number	Results	Toxicity Category
870.1100	Acute-oral	46378518	LD ₅₀ (♂ or ♀) ≥ 5,000 mg/kg LD ₅₀ Combined ≥ 5,000 mg/kg	IV
870.1200	Acute-dermal	Not applicable for proposed use pattern (Import tolerance)		
870.1300	Acute-inhalation	Not applicable for proposed use pattern (Import tolerance)		
870.2400	Acute-eye irritation-rabbit	Not applicable for proposed use pattern (Import tolerance)		
870.2500	Acute-dermal irritation-rabbit	Not applicable for proposed use pattern (Import tolerance)		
870.2600	Skin sensitization - guinea pig	Not applicable for proposed use pattern (Import tolerance)		

GDLN	Study Type/ Classification	Dose Levels	MRID	Results
870.3100	1997 13 WEEK FEEDING-RAT Acceptable/Guideline	ppm = 0, 200, 650, 2000 mg/kg/day = M: 0, 16.3, 49.7, 154 F: 0, 17.9, 58, 164	46387805	NOAEL (mg/kg/day) M: 16.3 F: 58 LOAEL (mg/kg/day): M: 49.7, based on testicular/epididymal effects (abnormal spermatids in the testes, and abnormal spermatogenic cells in the epididymides) F: 164, based on decreased body weights and fine vacuolation of the adrenal zona glomerulosa.
870.3100	2002 13 WEEK FEEDING-MOUSE Acceptable/Guideline	ppm = 0, 200, 450, 1000 mg/kg/day = M: 0, 33, 74, 163, 405 F: 0, 41, 93, 195, 483	46387802	NOAEL (mg/kg/day) M: 450 F: 483 LOAEL (mg/kg/day): not determined
870.3150	2001 13 WEEK FEEDING-DOG Acceptable/Guideline	mg/kg/day = 0, 15, 40, 100	46387803	NOAEL (mg/kg/day): M: 100, F: not determined LOAEL (mg/kg/day): M: not determined F: 15, based on reduced body weight (10%) and reduced body weight gain (62%)

Table 4.2 Subchronic, Chronic and Other Toxicity Profile for Ethaboxam

GDLN	Study Type/ Classification	Dose Levels	MRID	Results
870.3700	1997 DEVELOPMENTAL TOXICITY-RAT Acceptable/guideline	mg/kg/day = 0, 10, 30, 100, 300	46387808 46488701	<u>Maternal</u> : NOAEL (mg/kg/day): 30 <u>Maternal</u> : LOAEL (mg/kg/day): 100, based on hair loss (7/25) and increased water consumption (124%). <u>Developmental</u> : NOAEL (mg/kg/day): 30 LOAEL (mg/kg/day): 100, based on abnormal liver lobation (4 fetuses from 4 litters).
870.3700	1997 DEVELOPMENTAL TOXICITY-RABBIT Acceptable/Guideline	mg/kg/day = 0, 25, 75, 125	46490401	<u>Maternal</u> : NOAEL (mg/kg/day): 75 LOAEL (mg/kg/day): 125, based on inappetence (2 animals sacrificed), decreased food consumption (70%), and body weight loss (-73g vs. -16 controls). <u>Developmental</u> : NOAEL (mg/kg/day): 125 LOAEL (mg/kg/day): not determined

Table 4.2 Subchronic, Chronic and Other Toxicity Profile for Ethaboxam

GDLN	Study Type/ Classification	Dose Levels	MRID	Results
870.3800	2002 2-GENERATION REPRODUCTION- RAT Acceptable/Guideline	ppm = 0, 65, 200, 650 mg/kg/day = M: 0, 5.2, 16.2, 52.6 F: 0, 5.7, 17.6, 56.1	46387804	<p><u>Parental:</u> NOAEL (mg/kg/day) M/F: 16.2/17.6 LOAEL (mg/kg/day): M/F: 52.6/56.1, based on decreased pre-mating body weight gain of the F₀ and F₁ generation males (10.5-22% and 10.7-14.5%, respectively), decreased pre-mating body weight of the F₁ males and females (10.3-17.45 and 7-12.9%, respectively).</p> <p><u>Reproductive:</u> NOAEL (mg/kg/day) M: 16.2, F: 56.1 LOAEL (mg/kg/day): M: 52.6, based on testicular lesions and reduced fertility in F₁ males. F: not determined</p> <p><u>Offspring:</u> NOAEL (mg/kg/day) M/F: 16.2/17.6 LOAEL (mg/kg/day): M/F: 52.6/56.1, based on decreased body weight in male and female F₁ pups (13.1-15.7%), and decreased viability of the F₁ (14%) and F₂ (17%) males during lactation.</p>
870.4300	2002-104 WEEK COMBINED CHRONIC TOXICITY/CARCINO GENICITY-RAT Acceptable/Guideline	ppm = 0, 100, 300, 650 mg/kg/day = M: 0, 5.5, 16.4, 35.8 F: 0, 7, 21, 45.5	46387811	<p>NOAEL (mg/kg/day) M: 5.5 F: 21</p> <p>LOAEL (mg/kg/day): M: 16.4, based on adverse effects seen in the male reproductive organs (testes, epididymides, prostate, seminal vesicles) F: 45.5, based on decreased body weight (12%) and body weight gain (16%).</p> <p>Evidence of carcinogenicity Interstitial/Leydig cell adenoma at the highest dose tested (35.8/45.5 mg/kg/day)</p>

Table 4.2 Subchronic, Chronic and Other Toxicity Profile for Ethaboxam

GDLN	Study Type/ Classification	Dose Levels	MRID	Results
870.4100	2001-52 WEEK FEEDING-DOG Acceptable/Non- guideline	mg/kg/day = 0, 5, 10, 30	46387809	NOAEL (mg/kg/day): M/F = 30 LOAEL (mg/kg/day): not determined
870.4200	2003- 52 WEEK CARCINOGENICITY- MICE Acceptable/Guideline	ppm = 0, 100, 300, 900 mg/kg/day = M: 0, 12, 35, 117 F: 0, 14, 44, 135	46235628	NOAEL (mg/kg/day) M/F: 35/44 LOAEL (mg/kg/day): M/F: 117/135, based on decreased body weight (M/F=9%), body weight gain (M/F =20%) and food efficiency (M=16%; F = 19%) in both sexes, and liver toxicity in males. No evidence of carcinogenicity
870.5100	2004-BACTERIAL REVERSE MUTATION ASSAY Acceptable/Guideline		46378529	Negative
870.5300	2001- <i>IN VITRO</i> MAMMALIAN CELL GENE MUTATION TEST Acceptable/Guideline		46378530	Negative
870.5375	2001- <i>IN VITRO</i> MAMMALIAN CELL CHROMOSOME ABERRATION TEST Unacceptable/Guideline		46378531	LGC-30473 induced significant ($p < 0.01$) increases in chromosome aberrations and a marked increase in the mitotic index at a concentration of 250 $\mu\text{g}/\text{mL}$ (-S9) after a 3 hour exposure and at 100 $\mu\text{g}/\text{mL}$ after 19 hours of continuous exposure.
870.5395	2001-MAMMALIAN ERYTHROCYTE MICRONUCLEUS TEST (XDE-750) Acceptable/Guideline		46378532	Negative

Table 4.2 Subchronic, Chronic and Other Toxicity Profile for Ethaboxam

GDLN	Study Type/ Classification	Dose Levels	MRID	Results
870.7485	2003-METABOLISM AND PHARMOKINETICS- RAT Acceptable/Guideline	Thiazole or Thiophene radiolabeled mg/kg/day = Low dose: 10 High dose: 150 Thiazole radiolabeled Mg/kg/day = 10 Daily for 14 days	46378533	Excretion-Majority of the radiolabeled compound was excreted in the feces or urine within 48 hours of administration, regardless of radiolabel, dose, or sex. For both radiolabels, fecal and urinary excretion combined accounted for 96-104% of the administered dose. The main route of excretion was feces (66-74% of single or repeated administered low-dose), followed by urine (23-30% of the administered low-dose). Biliary excretion-thiazole radiolabeled compound absorbed in males and females within 48 hours; low dose = 71 and 72%, respectively, high-dose = 48 and 61%, respectively. After 48hrs, 79-94% compound absorbed depending upon the dose. Tissue distributions-minimal amounts (<1% of the dose) of the radiolabeled compound were retained in the tissues up to 120 hours post dosing. The thyroid generally contained the highest µg equivalents/g of the thiazole label, but only minimal amounts of the thiophene label.

