

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY  
DEPARTMENT OF PESTICIDE REGULATION  
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

ETHOFUMESATE

SB 950-346, Tolerance # 345

October 14, 1986

Revised 9/1/87, 10/24/88, 09/13/93, and 7/25/95

I. DATA GAP STATUS

Combined rat:	No data gap, no adverse effect
Chronic dog:	No data gap, no adverse effect
Onco hamster:	No data gap, no adverse effect
Repro rat:	No data gap, no adverse effect
Terato rat:	No data gap, no adverse effect
Terato rabbit:	No data gap, possible adverse effect
Gene mutation:	No data gap, no adverse effect

Chromosome: No data gap, no adverse effect

DNA damage: No data gap, no adverse effect

Neurotox: Not required at this time

-----**Note, Toxicology**

**one-liners are attached**

\*\* indicates acceptable study

**Bold face** indicates possible adverse effect

File name T950321

Revised by P. Iyer, 7/25/95

II. TOXICOLOGY SUMMARY

COMBINED RAT

\*\* 042 069 985767 068052 "The Effects of the Dietary Administration of NC 8438 to Male and Female Rats for Two Years," (Fisons Ltd., England, 1/76). Ethofumesate technical (Batch CR 4507; purity = 92.5%) was fed in the diet for 2 years to CFHB Wistar rats (40/sex/group) at 0 (60/sex), 8, 40, 200, 1000 or 5000 ppm (60/sex), equivalent to 0.5, 2.2, 10.5, 55 or 300 mg/kg during the first 6 weeks. **No adverse effect.** NOEL = 1000 ppm (55-83% mortality in 5000 ppm males; chronic nephritis, especially in males was a major cause of death; murine respiratory disease was observed in "every" rat; body weights were depressed 6% in males and 12% in females at termination--5000 ppm; hematology and clinical chemistry parameters were marginal--no electrolytes, cholesterol at 12 months only; 5/sex control and 5000 ppm only were analyzed at 12 months with no 18 month sampling; histopathology - no spinal cord; increased liver weights with no histopathological findings and no observable effects on clinical chemistry). No oncogenic effect was reported. The increase in liver weight with no accompanying histopathological findings was considered a possible adverse effect in an initial review (J. Remsen, 8/29/85). It has since been considered to be due to enzyme induction (J. Remsen, 8/25/87) and of questionable biological significance. The study was originally reviewed as unacceptable (no clinical observations; no periodic analysis of diet; no eye examination; insufficient clinical chemistry at 24 months). These issues have been addressed in a document submitted to CDFA (069 068052) and the study is now considered **acceptable**. M. Silva, 10/14/88.

EPA 1-liner: No core grade. Systemic NOEL = 1000 ppm (reduction in weight gain in females, relative liver weight increase (males), increase in mortality (11%, males; chronic nephritis), oncogenic NOEL > 5000 ppm (HDT)).

064 052349 Addendum to 042 985767: Composition of technical material.

064 052350 Addendum to 042 985767: "Ninety-day Dietary Toxicity Study of "Nortron" in the Wistar Rat." Doses were 0, 16, 80, 400, 2000 or 10,000 ppm with a NOEL of 400 ppm based on increased liver (reversible) and kidney weights in males. JG, 8/25/87.

032 985765 (1976, Fisons Ltd.) Duplicate of 042 985767, but missing appendices.

002, 008 985771 Six and twelve month interim report for 042 985767.

057 036545 Duplicate of 042 985767.

CHRONIC, DOG

\*\* 057 036544 "Nortron Technical (NC 8438) Toxicity Study in Beagle Dogs." Huntingdon Research Centre, England, 1/9/80; Ethofumesate, 97.1%; fed to 8/sex/group of Beagle dogs for two years at 0, 800, 4000 or 20,000 ppm (24, 113 or 626 mg/kg/day); initially reviewed as having a possible adverse effect on the liver with increased organ weight and elevated SAP and SGPT later in the study but no histopathological findings were reported - upon reconsideration, this was changed to negative for adverse effect based on the lack of microscopic findings supporting the weight increase. NOEL = 4000 ppm (increased organ weight). Acceptable. JR, 8/29/85, 12/2/85 and 9/1/87.  
EPA 1-liner: Guideline. NOEL = 4000 ppm (increased SGPT, SAP and liver weight.)

056 014856 (1980, Huntingdon Research) JR 8/29/85 Duplicate of 057 036544; missing appendices.

069 068054 "Determination of Ethofumesate (NC 8483) Dietary Concentrations in a Two Year Feeding Study With Dogs," (Fisons Agrochemical Division, 1/80). Analysis of dosing material in diet for 057 036544.

ONCOGENICITY, RAT

See COMBINED, RAT

ONCOGENICITY, MICE

008 985773 Not a chronic study, summary, duplicate of 002 985773.

ONCOGENICITY, HAMSTER

\*\* 058 036546 "A Carcinogenicity Study of (Technical) NC 8438 in Hamsters," Bio-Research Consultants, Cambridge, MA, 8/80; Ethofumesate, 90.8%; fed in the diet to Syrian hamsters, 50/sex/test group, 100/sex in control, at 0, 80, 400 or 2000 ppm; exposure began 1 week before mating of parents, continued through gestation, lactation and lifespan (84 - 98 weeks; sacrificed when group reached 60% mortality; NOEL = 400 ppm (increased liver weight without histopathological finding); initially reviewed as unacceptable based on lack of justification of dose selection with no overt toxicity but upgraded to Acceptable with submission of rebuttal in 066. Housed 5/cage. Use of hamsters is justified on basis they are less susceptible to disease, are sensitive to carcinogens and are acceptable by FIFRA. The initial notation of a possible adverse effect has been changed upon reconsideration as an indication of enzyme induction since there were no microscopic findings. JR(G), 2/2/85 and 8/87.

EPA 1-liner: Minimum. Oncogenic NOEL > 2000 ppm (HDT), systemic NOEL = 400 ppm (increased liver weight - F).

056 014855 Bio-Research Consultants, Cambridge, MA, 8/80 JR, 8/29/85. Duplicate of 058 036546; missing appendices.

069 068055 "Determination of Ethofumesate (NC 8438) Dietary Concentrations in a Carcinogenicity Study With Hamsters," (Fisons Agrochemical Division, 3/80). This volume contains an analysis of dosing material in diet for study 058 036546.

REPRODUCTION, RAT

\*\* 059 036547 "Technical NC 8438: Multigeneration Study in the Rat - Final Report," Life Science Research, Stock, Essex, England, 9/80; Ethofumesate, 97.8% technical; fed to CD rats, 30/sex/group, at 0, 200, 1000 or 5000 ppm for three generations, two litters; in second litter, 1/2 were sacrificed on day 21 and 1/2 were allowed to deliver. No adverse reproductive effect reported. Initially reviewed as unacceptable based on dose selection and limited number of animals for histopathology but upgraded to Acceptable based on reconsideration in response to the rebuttal in 064. Reproduction NOEL  $\geq$  5000 ppm, systemic NOEL = 1000 ppm (liver weights). JR(G), 12/3/85 and 8/87.  
EPA 1-liner: Minimum. Reproductive NOEL > 5000 ppm (HDT), teratology potential not defined (high incidence of hydrocephaly, maternal toxic NOEL > 5000 ppm, fetotoxic NOEL > 5000 ppm (HDT)).

056 014857 (1980, Life Science Research) JR, 8/29/85. Duplicate of 059 036547; missing the appendices.

069 068054 "Determination of Ethofumesate (NC 8438) Dietary Concentrations in a Multi-Generation Study With Rats," (Fisons Agrochemical Division, 4/79). This volume provided an analysis of dosing material in diet for study 059 036547.

TERATOLOGY, RAT

042 985778 "Effect of NC 8438 on Pregnancy of the Rat," Huntingdon Research Centre, 2/75; Ethofumesate (97.7% - see 064, #52212); given by oral gavage to 20/group CD rats at 0, 20, 40 or 80 mg/kg, days 6 - 15; Unacceptable (no justification of dose, high dose inadequate,); no adverse effect reported. Not upgradeable. NOEL not established - doses too low. J. Remsen, 8/29/85.

EPA 1-liner: No core grade. Teratogenic NOEL > 80 mg/kg (HDT), maternal NOEL > 80 mg/kg (HDT), fetotoxic NOEL > 80 mg/kg (HDT).

064 052212 Addendum to 042 985778: Composition of the technical material used in this study.

008 985776 (1975, Huntingdon Research) Duplicate of 042 985778.

077 097501, "Technical Ethofumesate: Oral Teratology (Developmental Toxicity) Study in the Rat", (R. Clark, Hazleton UK, Report #'s - Hazleton: 194/38. Nor-Am: Tox 90284. 5/10/91), technical ethofumesate, 97% purity, administered to 24 mated Sprague-Dawley Crl:CD(SD)BR females per group by gavage on gestation days 6 through 15 at 0 (1% w/v methyl cellulose in distilled water), 10, 100, and 1000 mg/kg/day. Dosing levels were based on a rangefinding study using pregnant females. Increased incidence of salivation at 1000 mg/kg/day is reported. Reported Maternal NOEL = 100 mg/kg/day (salivation at 1000 mg/kg/day). Reported Developmental NOEL = 1000 NOEL. Initially reviewed as unacceptable (H. Green, and P. Iyer, 9/13/93). Upgraded upon submission of data verifying dosing levels (P. Iyer, 7/25/95).

\*\* 345-082 127767 "Determination of ethofumesate concentrations in methyl cellulose suspensions for a preliminary dose range finding study and teratology study in the rat", (J.H.M. Bright, Nor-Am: Schering Agrochemicals Ltd, 12/15/93). The mean values for the analyzed suspensions were in the range of 98.9% to 110.2% of the nominal. These values are acceptable and the teratology study (077 097501) is now acceptable. No worksheet. P. Iyer, 7/25/95.

Note: Summary for this report (Page 9) is missing.

TERATOLOGY, RABBIT

\*\* 060 042071 "SN 49.913 (Ethofumesate) - Embryotoxicity Including Teratogenicity Study in the Rabbit After Daily Intra-gastric Administration From Day 6 to Day 18 of Gestation," Schering Ag, 1/28/86; Ethofumesate, no purity stated, Batch # CR 4905/10; given by oral gavage to 25/group at 0, 30, 300 or 3000 mg/kg/day, days 6 - 18 of gestation (day 0 = day of mating); increased mortality (11/25) in high dose group - dose selection was based on a range-finding study in pregnant rabbits; Developmental toxicity: delayed ossification at 300 and 3000 mg/kg, increased resorptions at 300 mg/kg; maternal NOEL = 300 mg/kg (abortion, death); Developmental NOEL = 30 mg/kg (resorptions and delayed ossification). Initially reviewed as unacceptable based on the lack of analyses of dosing solutions and historical controls. Upgraded to acceptable with submission of missing data in 066, 055483, 055484 and 055485. J. Parker, 5/2/86 and JG, 8/87.

066 055483 to 055485 Historical control data, analyses of dosing solutions and stability over 24 hours for 042071.

MUTATION, GENE

\*\* 059 036549 "Technical Ethofumesate: Mutagenic Activity in Salmonella typhimurium and Escherichia coli," Inveresk Research Int'l, 11/21/83; Ethofumesate, 97.4%; Salmonella

strains TA1535, TA1537, TA1538, TA98 and TA100; test article at 0, 33, 100, 333, 1000, 3300 or 10,000 ug/plate with and without rat liver activation, precipitation at two highest concentrations; triplicate plates, repeat trials; no increase in mutation frequency is reported. Acceptable. J. Remsen, 12/3/85.

056 014854 (1983, Inveresk Research Int'l) JR 8/23/85 Duplicate of  
059 036549; tables are missing.

MUTATION, CHROMOSOME

002 985780 "NC 8438: A Test for the Induction of Dominant Lethal Mutations in the Rat," Fisons Corp, 3/72; Ethofumesate, no purity stated; fed to 12 male Wistar rats for 13 weeks at 10,000 ppm followed by 4 weeks recovery; mated to 8 females. Unacceptable (protocol). No adverse effect reported. Also included in report is sodium methanesulphonate at 10,000 ppm for 13 weeks to 12 males followed by 1 week rest and mating 1:1 with 12 females. No adverse effect reported. J. Remsen, 8/29/85.  
EPA 1-liner: No core grade. Negative at 10,000 ppm (HDT).

042 985782 (1972, Fisons Corp.) Duplicate of 002 985780.

059 036548 (1972, Fisons Corp.) Duplicate of 002 985780.

\*\* 061 043028 "Technical Ethofumesate: Mouse Micronucleus Test," Huntingdon Research Centre Ltd. via FBC Limited, Chesterford Park Research Station, 12/11/85; Ethofumesate, 96.3% purity. 8100 mg/kg by gavage to 5 mice/sex/sacrifice time (24, 48 and 72 hours after dosing). No cytotoxicity, no mutagenicity. Complete. Acceptable. B. Davis, 10/10/86.

MUTATION, DNA

\*\* 071 070895 "T108: Technical Ethofumesate: Assessment of Unscheduled DNA synthesis Using Rat Hepatocyte Cultures," (Inveresk Research International, 4/28/88). Ethofumesate technical (96.3% purity; code/batch no. CR 4805/10) was used on primary cultures of adult rat hepatocytes (2 experiments using cells from different animals) at 0 (vehicle = DMSO), 1.56, 3.12, 6.25, 12.5, 25, 50, 100 and 200 ug/ml (quadruplicate wells) for 18-20 hours. Three coverslips/dose level were counted (50 cells/coverslip). **No adverse effect.** No increase in unscheduled DNA synthesis was observed at any concentration level. Positive controls functioned as expected. **Acceptable.** M. Silva, 10/24/88.

NEUROTOXICITY

Not required at this time.