

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

CARBOXIN

Chemical Code # 1755, Tolerance # 301
SB 950 # 143

July 16, 1987
Revised 1/30/90, 4/9/93, 5/2/94

I. DATA GAP STATUS

Chronic toxicity, rat:	No data gap, possible adverse effect.
Chronic toxicity, dog:	No data gap, no adverse effect.
Oncogenicity, rat:	No data gap, no adverse effect indicated.
Oncogenicity, mouse:	No data gap, possible adverse effect.
Reproduction, rat:	No data gap, possible adverse effect.
Teratology, rat:	No data gap, no adverse effect.
Teratology, rabbit:	No data gap, no adverse effect.

Gene mutation:	No data gap, no adverse effect.
Chromosome effects:	No data gap, possible adverse effect.
DNA damage:	No data gap, possible adverse effect.
Neurotoxicity:	Not required at this time.

Toxicology one-liners are attached.

All record numbers through 126310 were examined.

** indicates an acceptable study.

Bold face indicates a possible adverse effect.

File name: T940502

Revised by: S. Morris 5/2/94

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

COMBINED, RAT

**** 301-031; 092719;** "Combined Chronic Toxicity and Oncogenicity Study with Vitavax* Technical in Rats"; HLA 6111-106; D.F. Kehoe; Hazleton, Laboratories America, Inc., WI; 4/26/91. Dietary mixtures of Carboxin (Vitavax Technical, batch # 6L-854, 97.7% stated purity) were given for 102 weeks to 60 Crl:CD*SD rats/sex/group at 0, 20, 200, or 400 ppm for males and 0, 20, 300, or 600 ppm for females. Ten rats/sex/group were sacrificed and necropsied at week 52. Treatment-related effects were: decreased survival in males at 400 ppm (13/49) vs. controls (23/50); lower mean body weights for males at 200 and 400 ppm and females at 300 and 600 ppm with the respective mean body weights at 102 weeks being 93, 83, 91, and 79% of controls; increased water consumption in males at 200 and 400 ppm; changes in serum chemistry in males at 200 and 400 ppm; polyurea in males at 200 and 400 ppm; and lower urine pH in males at 400 ppm and females at 600 ppm. A possible adverse effect was indicated by treatment-related kidney effects in males at 200 and 400 ppm and females at 300 and 600 ppm: chronic nephritis, tubular cell degeneration and hyperplasia, and mineralization of the tubules. The NOEL for non-oncogenic effects was 20 ppm. There were no treatment-related oncogenic effects. The study was unacceptable (J. Kishiyama and S. Morris, 3/12/93) but upgraded with submission of HLA 6111-105 (S. Morris and J. Gee, 12/22/93).

301-035; 126309: This document contained HLA 6111-105. Evaluation of these data resulted in a change in study status for doc. # 301-031, rec. # 092719 (S. Morris, 12/22/93).

NOTE: The possible adverse effect was listed under the chronic toxicity test type because there were no treatment-related oncogenic effects.

CHRONIC TOXICITY, RAT

See COMBINED, RAT above.

301-012; 036496; "24-Month Dietary Administration -- Albino Rats, D-735 Technical", (Hazleton, 3/14/69). Carboxin technical, 100% pure, was administered in the feed to 60 control rats/sex and groups of 30 rats/sex at dose levels of 100, 200, or 600 ppm, all for 2 years with interim sacrifice of 5 rats/sex/treatment level or 10 control rats/sex at 6 and 12 months. No adverse effects reported. NOEL >600 ppm. **UNACCEPTABLE** and not upgradeable (dose selection). (J. Christopher, 5/6/85; F. Martz, 12/5/85).

EPA 1-liner: Core Supplementary (1/17/89).

301-013; 036497: Individual animal data for the study at DPR doc. # 301-012, rec. # 036496.

301-007; 017040: Partial duplicate of doc. # 301-012, rec. # 036496.

301-008; 047280: Summary of doc. # 301-012, rec. # 036496.

CHRONIC TOXICITY, DOG

** 301-030; 096697; "One Year Chronic Dietary Study in Dogs", Laboratory Project ID 399-100, E.I. Goldenthal, International Research and Development Corporation, 3/28/91. Carboxin (Vitavax Technical, lot # 905N185-FZ, 97%) was fed in the diets of 6 Beagle dogs/sex/group for 52 weeks at concentrations of 0, 40, 500, or 3000 ppm. The 3000 ppm diet was increased to 5000 ppm at week 7 and 7500 ppm at week 13. There were no treatment-related effects on mortality, clinical signs, feed consumption, ophthalmology, or gross or histopathology. There were treatment-related effects usually in both sexes and generally only at the highest dose: decreased body weight gains, altered hematology values, altered serum biochemistry, and increased serum enzymes. The NOEL was 40 ppm based on effects in females at 500 and 3000 ppm: decreased body weight gain and increased mean corpuscular volume and serum alkaline phosphatase. There was insufficient toxicity to identify a target organ. No adverse effect was indicated. The study was unacceptable because of an inadequate rationale for the doses (J. Kishiyama and S. Morris, 2/19/93) but upgraded to acceptable at this time by data in other acceptable studies that adequately characterize the toxicity of the test material (S. Morris and J. Gee, 5/2/94).

301-035; 126307: This document contains the group mean body weights of the dogs at six weeks. Evaluation of these data did not result in a change in study status for DPR doc. # 301-030, rec. # 096697. No worksheet was done (S. Morris, 5/2/94).

301-036; 126310; "A Four Week Oral Toxicity Study in the Dog of VITAVAX* Technical via Dietary Administration". Evaluation of these data did not result in a change in study status for DPR doc. # 301-030, rec. # 096697. See DPR Worksheet dated 5/2/94 (S. Morris, 5/2/94).

301-014; 036498; "Two-Year Dietary Administration -- Dogs, D735", (Hazleton, 2/5/69). DK-735 technical (carboxin, assumed 100%) was administered in the feed to 6 control dogs/sex and groups of 4 dogs/sex at dose levels of 100, 200, or 600 ppm, all for 2 years with interim sacrifice of 1 dog/sex/dose at 1 year; no effects, numerous deficiencies, insufficient

information for NOEL. **UNACCEPTABLE** and not upgradeable. (J. Christopher, 5/6/85; F. Martz, 12/9/85; 6/5/87).

EPA 1-liner: Core Supplementary (upgradeable), as of 1/17/89.

301-022; 050920: Rebuttal and supplemental information to 036498. Supplemental information includes individual necropsy and histopathology data on selected animals; does not upgrade study (no status change). (F. Martz, 6/5/87).

301-007; 017039: Partial duplicate of DPR doc. # 301-014, rec. # 036498.

ONCOGENICITY, RAT

See COMBINED RAT above.

ONCOGENICITY, MOUSE

**** 301-010; 036493;** "Lifetime Carcinogenicity Study in Mice" (IRDC, 8/20/82). Carboxin technical (>99% pure) was administered in the feed to 75 control mice/sex and groups of 50 mice/sex at levels of 50, 2500, or 5000 ppm for 19 months. Increased mortality in females; hepatocellular hypertrophy at 2500 and 5000 ppm in both sexes with a greater incidence in males; significant increase in pulmonary adenomas/alveolar-bronchiolar adenomas in high dose males only, 34% vs. 17% in concurrent controls or 12% in historical controls. Possible **ADVERSE EFFECT**. Upgraded to **ACCEPTABLE** by supplemental information (see 022, below). (F. Martz, 12/4/85 and 6/8/87).

301-011; 036495: Appendices to DPR doc. # 301-010, rec. # 036493.

301-022; 050921;

301-022; 050922: Supplemental information to doc. # 301-010, rec. # 036493; includes test article characterization data, study protocol and amendments (F. Martz, 6/8/87).

301-023; 057727: Supplemental information to doc. # 301-010, rec. # 036493; individual food consumption raw data (F. Martz, 6/17/87).

301-007; 023106: Summary of DPR doc. # 301-010, rec. # 036493.

301-025; 063907: This document contains historical control incidences of lung adenomas in male Charles River CD-1 mice. No worksheet was done (see memo dated 1/28/88).

REPRODUCTION, RAT

**** 301-032; 092720;** "Two-Generation Reproduction Study with Vitavax* in Rats (Two Litters/Generation)"; HLA 6111-128; D.F. Kehoe; Hazleton, Laboratories America, Inc., Madison, WI; 4/11/91. Dietary mixtures of Carboxin (Vitavax Technical, lot # 812N465FZ, . 97.7%

purity) of 0, 20, 200, or 400 ppm for males or 0, 20, 300, or 600 ppm for females were continuously administered to 25 adult Crl:CD*BR rats/sex/group (F0 generation) for at least 10 weeks pre-mating then through mating, gestation, lactation, and the rest period for 2 litters (F1a, F1b). Twenty-five F1b weanlings/sex/group were similarly exposed and produced the F2a and F2b litters. Exposures during mating were at the females dietary concentrations. A treatment-related effect was decreased adult body weight gains in both sexes at the highest doses with body weights always being > 85% of controls. A **possible adverse effect** was indicated by kidney pathology in both sexes of the F1b generation at the middle and high doses (NOEL = 20 ppm). The NOEL's for reproductive effects in males and females were respectively 400 and 600 ppm based on the lack of significant treatment-related effects on reproductive variables. The study was unacceptable (J. Kishiyama and S. Morris, 4/4/93) but upgraded by submission of an adequate rationale for the doses used and documentation of the F1b dosing protocol (S. Morris and J. Gee, 12/28/93).

301-035; 126308: This document contains documentation of the F1b dosing protocol. Evaluation of these data resulted in a change in study status for doc. # 301-031, rec. # 092719 (S. Morris, 12/28/93).

301-035; 126309: This document contains a subchronic study. Evaluation of these data resulted in a change in study status for doc. # 301-031, rec. # 092719 (S. Morris, 12/28/93).

301-014; 036501; "Three-Generation Reproduction Study -- Rats, D-735 Technical" (Hazleton, 8/9/68). Carboxin technical, 100% pure, administered in the feed to 30 control rats/sex and groups of 10 males and 20 females at dose levels of 0, 100, 200, or 600 ppm for 3 generations. Slight growth retardation in 600 ppm nursing pups, all 3 generations; NOEL = 200 ppm. Incomplete (missing some summary and individual data). **UNACCEPTABLE** and not upgradeable by rebuttal dated 11/14/86 (in volume #301-022) or any other information (J. Christopher, 5/6/85; F. Martz, 12/5/85 and 6/8/87).
EPA 1-liner: Core Supplementary (1/17/89).

301-007; 017032: Partial duplicate of doc. # 301-014, rec. # 036501.

301-003; 047279: Summary of doc. # 301-014, rec. # 036501.

TERATOLOGY, RAT

** 301-028; 074733; "Developmental Toxicity Study in Rats", (IRDC, Lab. Product I.D. 399-077, 5/31/89). Carboxin, 97.0%, Lot #NI 24064F0, was administered by gavage to groups of 25 female Sprague-Dawley COBS CD rat at dose levels of 0 (0.5% methylcellulose), 10, 90 and 175 mg/kg/day on days 6 through 15 of gestation. Decreased weight gain, reduced food consumption, and alopecia were observed at the mid and high doses. Decreased fetal weight was noted at 175 mg/kg/day. Maternal NOEL = 10 mg/kg/day (decreased weight gain/food consumption; alopecia); Developmental NOEL = 90 mg/kg/day (decreased fetal weight). The study is ACCEPTABLE and no adverse health effect is noted (J. Kishiyama, 9/13/89; G. Chernoff, 1/29/90).

301-014; 036499; "Teratological Evaluation of Vitavax Technical in Sprague Dawley Rats", (FDRL, 9/14/77). Carboxin technical, 99.5%, was administered by oral gavage in corn oil to groups of 22-26 pregnant rats at dose levels of 0 (vehicle control), 4, 20, or 40 mg/kg/day, or 250 mg aspirin/kg/day (positive control) on days 6-15 of gestation (plug=day 0). No maternal or developmental toxicity, NOEL>40 mg/kg/day (HDT). **UNACCEPTABLE** and not upgraded by rebuttal and additional information - no MTD (F. Martz, 12/6/85 and 6/4/87).

EPA 1-liner: Core Minimum.

301-022; 050923: Rebuttal and supplemental information to 036499 (F. Martz, 6/4/87).

301-007; 017031: Partital Duplicate of doc. # 301-014, rec. # 036499.

TERATOLOGY, RABBIT

** 301-014; 036500; "Teratology Study in Rabbits (Vitavax Technical)", (IRDC, 11/12/81). Carboxin technical, 98.9%, in 0.5% CMC was administered to groups of 16 Dutch Belted rabbits by oral gavage at doses of 0 (vehicle control), 75, 375 or 750 mg/kg/day on days 6 to 27 of gestation. Effects observed included abortions in 3 of 16 litters at 750 mg/kg, and 1 of 15 litters at 375 mg/kg between gestational days 27 and 28; weight loss one week prior to the abortions in 3 of the 4 females; and decreased fecal production at 375 and 750 mg/kg/day. Since the increased abortions occurred only in the presence of apparent maternal toxicity, they are not considered to constitute a possible adverse health effect. No signs of developmental toxicity or fetal malformations were observed at any of the dose levels tested. Maternal NOEL=75 mg/kg/day (increased abortions, decreased weight gain and fecal production), Developmental NOEL=750 mg/kg/day (no effects reported). Initially reviewed as unacceptable but possibly upgradeable with submission of the original material disposition records and a retrospective analysis of the dosing suspension (F. Martz, 12/6/85 and 6/4/87). Supplemental report no. 074732 satisfies this requirement, and the study is upgraded to **ACCEPTABLE** status. G. Chernoff, 11/2/89.

EPA 1-liner: Core Minimum.

301-022; 050837: Supplemental information to 036500 (F. Martz, 6/4/87).

301-028; 074732: supplemental to 036500; material inventory data sheet and dose solution analysis results for homogeneity and stability (G. Chernoff, 11/2/89).

301-007; 017030: Partital Duplicate of doc. # 301-014, rec. # 036500.

GENE MUTATION

** 301-015; 036502; "Mutagenicity Evaluation of Technical Grade Vitavax Lot No. 956, 98+% in the Ames Salmonella/Microsome Plate Test", (Litton Bionetics, 9/82). Carboxin (98%), Salmonella strains TA1535, 1537, 1538, 98 and 100; tested at 0. 1.0, 10, 100, 500, 1000, 2500

or 5000 µg/plate with and without rat liver activation, in triplicate; no mutagenic effect reported. Complete, **ACCEPTABLE** (J. Gee, 12/11/85).

301-007; 017033: Partial duplicate of doc. # 301-015, rec. # 036502.

301-015; 036503; "Ames Test Vitavax Technical, Mutagenicity Evaluation of D-735", (Litton Bionetics, 5/77). Gene Mutation with Salmonella strains TA1535, 1537, 1538, 98, and 100. Carboxin technical, purity not given, 0-500 µg/plate, with and without rat liver S-9 activation, single plate, one trial; no mutagenic effect reported, no cytotoxicity information. **UNACCEPTABLE**. (single plate) - not upgradeable (J. Gee, 12/11/85).

301-007; 017037: Partial duplicate of doc. # 301-015, rec. # 036503.

CHROMOSOME EFFECTS

** 301-015; 036507; "In Vivo Bone Marrow Chromosome Study in Rats, Vitavax", (Hazleton (VA), 6/27/85). Carboxin technical, 98% pure, by oral gavage in CMC to 20/sex/dose once at 4000, 2000, 750 or 0 mg/kg; 5/sex/level at 800, 400, 100 or 0 mg/kg for 5 consecutive doses with sacrifice at 6 hours post-treatment. Doses based on preliminary studies included with report. No adverse effects in aberrations, chromosome number, or mitotic indices were reported. **ACCEPTABLE** (J. Gee, 12/12/85).

** 301-015; 036506; "In Vivo Bone Marrow Chromosome Study in Rats, Vitavax", (Hazleton, (VA), 7/29/83). Carboxin technical, 98% pure, in CMC by oral gavage once at 2000, 660, 200, or 0 mg/kg to 20/sex/level with sacrifice at 6, 12, 24 and 48 hours. No statistically significant effect reported on aberrations, chromosome number, or mitotic index. **ACCEPTABLE** (J.R. Gee, 12/12/85).

301-007; 017036: Partial duplicate of doc. # 301-015, rec. # 036506.

**** 301-015; 036505;** "Mutagenicity Evaluation of Technical Grade Vitavax, Lot 956, 98% a.i., in an In Vitro Cytogenetic Assay Measuring Chromosome Aberration Frequencies in Chinese Hamster Ovary Cells", (Litton Bionetics, 9/82). CHO cells with and without rat liver S9 activation, 0-1.67 mg/ml (5 concentrations) without S9 (2 trials) or 0-1.2 mg/ml (5 concentrations) with S9 (3 trials), 12 hour harvest only; statistically significant increase in aberrations/cell and % cells with aberrations, with activation. Initially reviewed as unacceptable but upgradeable. Reconsideration of the study, in view of the positive response and harvesting at 12 hours when cells would be in M_1 , upgrades it to **ACCEPTABLE** status (J. GEE, 12/12/85 and 6/16/87).

301-007; 017034: Partial duplicate of doc. # 301-015, rec. # 036505.

COMMENT: The findings of a positive cytogenetic effect in vitro (Record No. 036505) but not in vivo (Record nos. 036506 and 036507) is substantiated in a survey of literature on 216 compounds (Thompson, E.D., Environmental Mutagenesis (1986) 8; 753-767). The conclusion of the author was that a negative test in vitro with activation is highly predictive of a negative test in vivo but a high incidence of "false positives" occurs in vitro. With carboxin, however, there is a positive test for unscheduled DNA synthesis (Record NO. 036504) substantiating an effect on chromosome/DNA in vitro and a possible oncogenic effect is reported in mice (Record Nos. 036493 and 036495). There is a possibility that in vivo the carboxin does not reach the bone marrow due to inactivation or barriers since there was no effect reported on mitotic index at doses to 2 g/kg in rats with sacrifices at 4 post-treatment times (Record No. 036506).

DNA DAMAGE

**** 301-015; 036504;** "Evaluation of Vitavax Technical Grade in the Primary Rat Hepatocyte Unscheduled DNA Synthesis Assay", (Litton Bionetics, 10/82). Carboxin technical, 98% pure, at 0-256 μ g/ml (9 concentrations) for 18 hours; 256 μ g/ml was limit of toxicity and solubility;

increased grain with increasing concentration are reported as is % ≥ 6 grains/nucleus increased. **ACCEPTABLE.** (J.R. GEE, 12/11/85).

301-007; 017035: Partial duplicate of doc. # 301-015, rec. # 036504.

NEUROTOXICITY

Not required at this time.

MISCELLANEOUS

301-005; 951486; "5,6-Dihydro-2-methyl-1, 4-oxathiin-3-carboxanilide (Carboxin), Pesticide Registration Standard", 3/81.

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301-025	063907
301-028	074732
301-028	074733
301-031	092719
301-032	092720
301-030	096697
301-035	126307
301-035	126308
301-035	126309
301-036	126310