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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, DC 20460

OFFICE OF
PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: California Department of Food and Agriculture - EPA Toxicology review for Carboxin (Tox. Chem. # 165A)

FROM: Whang Phang, Ph.D. 1/17/89
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THRU: K. Clark Swentzel 1/17/89
Acting Section Head
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and

Marcia van Gemert, Ph.D. 1/17/89
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TO: William Burnam, Acting Division Director
Health Effects Division (TS-769C)

The following responses are provided for each specific deficiency identified by the Medical Toxicology Branch of the California Department of Food and Agriculture:

1/ Study Type: Three-generation reproduction study in rats. Project No. 798-104; MRID No. 00003037; August 9, 1968.

Deficiency: Incomplete (missing some summary and all individual data)

EPA Response: This study was evaluated by the Toxicology Branch in 1969, however, it was never given a core-grade. Subsequently, the Registration Standard (1981) indicated that this study met data requirements. This reviewer has evaluated a copy of the submitted report, which consists of 22 pages and includes only summary data. The selected dosages (100, 200 and 600 ppm) do not appear to be appropriate. Therefore, this study should be classified Core-supplementary.

Conclusion: EPA also concludes that this study represents a data gap.

Core-grade: Changed to supplementary from no classification.

2/ Study Type: Chronic toxicity/oncogenicity study in rats. Project No. 798-102; MRID No. 00003031; March 14, 1969.

Deficiency: No effects reported (MTD not attained)

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EPA Response: This study was also evaluated in 1969 without assigning a Core-classification. The Registration Standard indicated that the data from this study were "sufficient to satisfy the requirement for a chronic feeding study" and that no additional data from a chronic toxicity/oncogenicity in rats was required.

This reviewer evaluated this study and found the following deficiencies:

a) The highest dose did not represent the maximum tolerated dose (MTD).

b) The number of rats/sex/dose was too low to adequately evaluate the oncogenic potential of the test agent. The study initially used 30 rats/sex/dose; of these, 5 rats/sex/treated group and 10 control rats/sex were sacrificed at 6 and 12 months during the study. Only 50% of the high-dose rats survived at 18 months and none of the high-dose rats were alive at the termination of the study.

c) The actual dosages of test material ingested by rats in the treated groups was questionable. The test report author stated that the chemical is a powder which has a tendency to "ball up". Therefore, it is unlikely that the batches of test material/diet mixtures were homogeneous.

Conclusion: EPA also concludes that this study represents a data gap.

Core-grade: Changed to supplementary from no classification

3/ Study Type: Two-year feeding study in dogs. Project No. 798-103; MRID No. 00003030; June 14, 1969.

Deficiency: CDFA indicated that there were numerous deficiencies in the study but specific examples were not given.

EPA Response: This study, which was initially evaluated in 1969, has never been given a core-grade by the Agency. The Toxicology Chapter of the Registration Standard for Carboxin did not mention this study.

This reviewer re-evaluated this study and found the following deficiencies:

a) No basis for dose selection (100, 200 and 600 ppm) was given. No apparent adverse effects from the test material were observed.

b) As indicated in the chronic/oncogenicity study in rats above, the test material had a tendency to "ball up" in the diet. The study report did not indicate if a limited quantity of the diet mixture, which was totally consumed, was provided daily. If this were true, then the lack of homogeneity of the test material in the diet would not be a critical problem.

c) The study report did not give the age of the dogs used in this study.

Conclusion: CDFA did not provide specific deficiencies for this study. TB identified three deficiencies above, therefore, this study represents a data gap.

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Core-classification: Changed to supplementary from no classification (upgradable if noted deficiencies could be satisfied).

4/ Study Type: Teratogenicity Study in Rats. FDRL, September 14, 1970.

Deficiency: None specified

EPA Response: The Agency does not consider this study a data gap.

Core-classification: minimum (no change; no deficiencies cited by CDFA to consider)

5/ Study Type: Teratogenicity Study in Rabbits. Report No. 399-043; MRID No. 246323; November 2, 1981.

Deficiency: None specified

EPA Response: The Agency does not consider this study a data gap.

Core-classification: guideline (no change; no deficiencies cited by CDFA to consider)

CALIFORNIA DEPARTMENT OF FOOD AND AGRICULTURE
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

CARBOXIN

SB95C-143, Tolerance # 301

July 16, 1987

I. DATA GAP STATUS

Chronic rat: data gap, unacceptable study, no adverse effect indicated (also see "Combined rat" below)

__ Chronic dog: data gap, unacceptable study, no adverse effect indicated

__ Combined rat: data gap (study started 5/87)

Oncogenicity mouse: data gap filled, possible adverse effect

__ Reproduction rat: data gap, unacceptable study, possible adverse effect indicated

Teratology rat: data gap, unacceptable study, no adverse effect indicated

__ Teratology rabbit: data gap, unacceptable study, no adverse effect indicated

Gene mutation: data gap filled, no adverse effect

Chromosomal aberration: data gap filled, possible adverse effect

DNA damage: data gap filled, possible adverse effect

Delayed neurotoxicity: not required at this time

.....

Filename: SB143SUM.FM
Tox index by N. Hughett

Toxicology one-liners attached: "**" indicates an acceptable study. "Bold face" of volume/record numbers indicates a possible adverse effect.

II. TOXICOLOGY ONE-LINERS

CHRONIC RAT (also see "Combined Rat" below)

301-012&013, 36496-36497; "24-Month Dietary Administration--Albino Rats, D-735 Technical, Final Report," Hazleton, 3/14/69; carboxin technical, "100% pure," in the feed at 600, 200, or 100 to 30/sex/level and 0 ppm to 60/sex/level for 2 years, with interim sacrifice of 5/sex/treated level or 10/sex/control at 6 and 12 months; no effects reported, NOEL>600 ppm. UNACCEPTABLE and not upgradable. CDFA review 5/6/85 by J. Christopher and 12/5/85 by F. Martz.

301-007, 17040; Partial duplicate (3 pages) of record #36496 in 301-012. CDFA review 5/6/85 by J. Christopher.

CHRONIC DOG

301-014, 36498; "Two-Year Dietary Administration--Dogs, D-735, Final Report," Hazleton, 2/5/69; DK-735 technical (carboxin, assumed 100%) in the feed at 600, 200 or 100 ppm to 4 dogs/sex/level and 0 ppm to 6 dogs/sex/level for 2 years with interim sacrifice of 1/sex/level at one year; no effects, numerous deficiencies, insufficient information for NOEL. UNACCEPTABLE--not upgradable by this (see record #50920) or other supplemental information. CDFA review 5/6/85 by J. Christopher, and 12/9/85 and 6/5/87 by F. Martz.

301-022, 50920; Rebuttal and supplemental information to -014, 36498; Supplemental information includes individual necropsy and histopathology data on selected animals; does not upgrade study, no status change. CDFA review 6/5/87 by F. Martz.

301-007, 17039; Partial duplicate (5 pp) of record #36498 in 301-014. CDFA review 5/6/85 by J. Christopher.

COMBINED RAT

301-022 (cover letter); New study to replace unacceptable chronic study, to be started May, 1987, at Hazleton (WI).

ONCOGENICITY MOUSE

301-010 and -011, 36493 and 36495; "Lifetime Carcinogenicity Study in Mice," IRDC, 8/20/82; Carboxin technical (>99% pure) in the feed at 5000, 2500 or 50 ppm to 50/sex/level and 0 ppm to 75/sex/level for 19 months; increased female mortality and hepatocellular hypertrophy, M>F, @ 5000 and 2500 ppm; significant increase in pulmonary adenomas/alveolar-bronchiolar adenomas, 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). CDFA review 12/4/85 and 6/8/87 by F. Martz.

301-022, 50921-50922; Rebuttal and supplemental information to 301-010 & 011, 36493-36495; Supplemental information includes test article characterization data and study protocol and amendments: Status changed to complete and acceptable. CDFA review 6/8/87 by F. Martz.

301-023, 57727; Supplemental information to 301-010 & 011, 36493 and 36495; consists of individual food consumption raw data. CDFA review 6/17/87 by F. Martz.

301-007, 23106; Summary (one paragraph) of record #36943 in 301-010. CDFA review 5/6/85 by J. Christopher.

REPRODUCTION/FERTILITY RAT

301-014, 36501; "Three-Generation Reproduction Study--Rats, D-735 Technical," Hazleton, 8/9/68; carboxin technical, "100 % pure," in the feed at 600, 200, or 100 ppm to 10 males/level and 20 females/level, and 0 ppm to 30/sex, for 3 generations; slight growth retardation in 600 ppm nursing pups, all 3 generations; NOEL=200 ppm. Incomplete (missing some summary and all individual data); UNACCEPTABLE and not upgradable by rebuttal dated 11/14/86 (in volume #301-022) or any other information. CDFA review 5/6/85 by J. Christopher, and 12/5/85 and 6/8/87 by F. Martz.

301-007, 17032; Partial duplicate (2 pages) of record #36501 in 301- CDFA review 5/6/85 by J. Christopher.

RAT TERATOLOGY

301-014, 36499; "Teratologic Evaluation of Vitavax Technical in Sprague Dawley Rats," FDRL, 9/14/77; carboxin technical, 99.5%, by oral gavage in corn oil at 40, 20, 4, or 0 mg/kg/day, or 250 mg aspirin/kg/day (positive control), to 22-26 pregnant/level on days 6-15 (plug=day 0), with kill on day 20; no maternal or developmental toxicity, NOEL>40 mg/kg/day (HDT). UNACCEPTABLE and not upgraded by rebuttal and additional information - no MTD. CDFA review 12/6/85 and 6/4/87 by F. Martz.

301-022, 50923; Rebuttal and supplemental information to -014, 36499 does not upgrade study, no status change. CDFA review 6/4/87 by F. Martz.

301-007, 17031; Partial duplicate (2 pages) of record #36499 in 301-014. CDFA review 5/6/85 by J. Christopher.

RABBIT TERATOLOGY

301-014, 36500; "Teratology Study in Rabbits (Vitavax Technical)" IRDC, 11/12/81; carboxin technical, 98.9% pure, by oral gavage in 0.5% CMC at 750, 375, 75, or 0 mg/kg/day to 16/level on days 6-27 (insem.=day 0) with kill on day 28; abortion in 3/16 @ 750 and 1/15 @ 375 mg/kg, days 27-28, with weight loss in 3/4 abortees in prior week; intact fetuses normal; soft stool @ 750, reduced stool @ 750 and 375 mg/kg; no malformations or developmental toxicity. Maternal NOEL=75 mg/kg/day, developmental NOEL>750 mg/kg/day. UNACCEPTABLE and not upgraded by supplemental information.

Could be UPGRADABLE with retrospective dosing suspension analyses and original material disposition records. CDFA review 12/6/85 and 6/4/87 by F. Martz.

301-022, 50837; Rebuttal and supplemental information to -014, 36500; does not upgrade study, no status change. CDFA review 6/4/87 by F. Martz.

301-007, 17030; Partial duplicate of -014, 36500 (2 pages). CDFA review 5/6/85 by J. Christopher.

MUTAGENICITY-GENE MUTATION

** *301-015, 36502; "Mutagenicity Evaluation of Technical Grade Vitavax Lot No. 956, 98+% In The Ames Salmonella/Microsome Plate Test, Final Report," 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 ug/plate with and without rat liver activation, in triplicate; no mutagenic effect reported. Complete, ACCEPTABLE. CDFA review 12/11/85 by J.R. Gee.*

301-007, 17033; Partial duplicate of -015, 36502 (2 pages). CDFA review 5/6/85 by J. Christopher.

301-015, 36503; "Ames Test Vitavax Technical, Mutagenicity Evaluation of D735, Final Report," Litton Bionetics, 5/77; Gene mutation with [redacted] strains TA1535, 1537, 1538, 98, and 100; carboxin technical, purity not given, 0-500 ug/plate, with and without rat liver S9 activation, single plate, one trial; no mutagenic effect reported, but no cytotoxicity information. UNACCEPTABLE. No repeat trial--not upgradable. CDFA review 12/11/85 by J.R. Gee.

301-007, 17037; Partial duplicate (2 pages) of -015; 36503. CDFA review 5/6/85 by J.P. Christopher.

MUTAGENICITY-CHROMOSOMAL ABERRATION

** *301-015, 36507; "In Vivo Bone Marrow Chromosomal Study in Rats, Vitavax, Final Report," Hazleton (VA); 6/27/85; chromosomal aberration; carboxin technical, 95% pure, by oral gavage in CMC to 20/sex/level once at 4000, 2000, 750, or 0 mg/kg with sacrifice of 5/sex/level at 6, 12, 24, or 48 hours, or 5 consecutive doses to 5/sex/level at 800, 400, 100, or 0 mg/kg with sacrifice at 6 hours; doses based on preliminary studies included with report; no adverse effects in aberrations, chromosome number, or mitotic indices are reported. ACCEPTABLE. CDFA review 12/12/85 by J.R. Gee.*

** *301-015, 36506; "In Vivo Bone Marrow Chromosome Study in Rats, Vitavax, Final Report," Hazleton (VA), 7/29/83; chromosomal aberration; 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. CDFA review 12/12/85 by J.R. Gee.*

301-007, 17036 Partial duplicate -015, 36506 (2 pages). CDFA review 5/6/85 by J. Christopher.

301-015, 36505: "Mutagenicity Evaluation of Technical Grade Vitavax, [illegible] In An In Vitro Cytogenetic Assay Measuring Chromosome Aberration Frequencies in Chinese Hamster Ovary Cells," Litton Bionetics, [illegible]. 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 (2 trials). 12 hour harvest only; statistically significant increase in aberrations/cell and % cells with aberrations, with activation. Initially reviewed as unacceptable but upgradable. Reconsideration of the study, in view of the positive response and harvesting at 12 hours when cells would be in M, upgraded it to ACCEPTABLE status. CDFA review 12/12/85 and 6/16/87 by J.R. Gee.

301-015, 37034: Partial duplicate (2 pages) of -015, 36505. CDFA review [illegible] by J. Christopher.

COMMENT: The finding of a positive cytogenetic effect in vitro (Record No. 36505) but not in vivo (Record Nos. 36506 and 36507) is substantiated in a survey of the 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. 36504) substantiating an effect on chromosomes/DNA in vitro and a possible oncogenic effect is reported in mice (Record Nos. 36493 and 36495). 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 the mitotic index at doses to 2 g/kg in rats with sacrifices at [illegible] post-treatment times (Record No. 36506).

MUTAGENICITY-DNA DAMAGE

301-015, 36504: "Evaluation of Vitavax Technical Grade in the Primary Rat Hepatocyte Unscheduled DNA Synthesis Assay," Litton Bionetics, 10/82: carboxin technical, 96% pure, at 0-256 ug/ml (9 concentrations) for 18 hours. 256 ug/ml was limit of toxicity and solubility; increased grains with increasing concentration are reported as is % ≥6 grains/nucleus increased. ACCEPTABLE. CDFA review 12/11/85 by J.R. Gee.

301-015, 37035: Partial duplicate (2 pages) of -015, 36504. CDFA review [illegible] by J. Christopher.

DELAYED NEUROTOXICITY

[illegible] required at this time.

MISCELLANEOUS

301-015, 45[illegible]: "5,6-Dihydro-2-methyl-1, 4-oxathiin-3-carboxanilide [illegible] Pesticide Registration Standard," 3/81.

FILE [illegible] SEQUENCE #:
DATE [illegible]