

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY  
DEPARTMENT OF PESTICIDE REGULATION  
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA  
CARBARYL

Chemical Code # 000105, Tolerance # 00169  
SB 950 # 142

September 14, 1987

Revised 10/25/88, 3/05/90, 7/31/90, 1/24/92, 9/7/93, 12/20/93, 1/28/98, 3/6/98, 6/28/99, 10/22/99,  
9/20/00 and 1/7/02

I. DATA GAP STATUS

Chronic rat:	No data gap, possible adverse effects
Chronic dog:	No data gap, no adverse effect
Oncogenicity rat:	No data gap, possible adverse effects
Oncogenicity mouse:	No data gap, possible adverse effects
Reproduction rat:	No data gap, no adverse effect
Teratology rat:	No data gap, no adverse effect
Teratology rabbit <sup>c, d</sup> :	No data gap, no adverse effect
Gene mutation <sup>a</sup> :	No data gap, no adverse effect
Chromosome mutation <sup>a</sup> :	No data gap, possible adverse effects
DNA damage <sup>a</sup> :	No data gap, no adverse effect
Neurotoxicity:	Not required at this time <sup>b</sup>

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**Note, Toxicology one-liners are attached**

\*\* indicates acceptable study.

**Bold face** indicates possible adverse effect.

File name: T020107

Original Toxicology Summary prepared by F. Martz, 9/14/87; revised by J. Gee, 10/88, 3/90,  
7/31/90 and 1/24/92. Updated by Kellner, 9/7/93 and 12/20/93. Revised by Gee, 1/28/98, 3/6/98,  
6/28/99, 10/22/99, 9/20/00 NS 1/7/02.

Rectified with DPR Library printout through volume 169-396, record # 177090.

<sup>a</sup> The data base for genotoxicity on file at DPR may not coincide with that of EPA. Collectively, EPA  
judged the studies to demonstrate a weakly positive response.

<sup>b</sup> There is a developmental neurotoxicity study on file with no adverse developmental effects  
reported.

<sup>c</sup> Data gap previously filled with multiple studies. See T990628.

<sup>d</sup> There are two studies with dogs on file that show possible adverse effects.

## II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

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

## RAT CHRONIC

099 000719, "Chronic Oral Feeding of SEVIN to Rats", No author, (Mellon Institute of Industrial Research, University of Pittsburgh, Report # 21-88, 10/6/58) Sevin, purity not provided, was fed in the diet for 24 months at 0 (ground Purina Laboratory Chow Meal), 0.005 (50), 0.01 (100), 0.02 (200), and 0.04 (400) % (ppm) with 20 CFN rats per sex per group. Interim sacrifices were performed at 6 months (four per sex per group at 0, 0.02 (200), and 0.04 (400) % (ppm)), 9 months (four per sex per group at 0, 0.02 (200), and 0.04 (400) % (ppm)), and 12 months (six or 8 per sex per group). At the high dose, decreased body weight gain in males, "cloudy swelling" of kidney tubules at 1 year sacrifice, and "cloudy swelling" of central hepatic cords at two years was noted. The changes are equivocal. Chronic NOEL = 200 ppm, NOAEL =  $\geq$  400 ppm. Uncorrectable deficiencies. UNACCEPTABLE and not upgradeable (insufficient numbers at termination, adequacy of high dose not demonstrated, incomplete necropsy and histopathology). (J. Schreider, 5/9/85 and F. Martz, 5/5/87). Re-examined by Green and Gee, 1/24/92.

EPA One-liner: Systemic NOEL = 200 ppm, LEL = 400 ppm (HDT; decreased weight gain in males, kidneys - cloudy swelling of convoluted and loop tubules, liver - cloudy swelling of hepatic cords about central vein). Core grade: minimum for chronic study, supplementary for oncogenicity study.

154, Tab C, Section II, pp 1-3: Rebuttal to #000719 above. Study can not be upgraded because of uncorrectable deficiencies, i.e., insufficient group size, no feed analysis, no ophthalmoscopic examinations, no evidence of MTD. Based on these considerations, it would be useless to address the rebuttal point by point. No status change. F. Martz, 8/7/87.

157 & 158, 050433 & -34: Supplemental information to #000719 above consisting of copies of laboratory notebooks and pathology records.

Note: The final report from a recently completed combined chronic/oncogenicity study in rats (HWA Study #656-139) has been submitted by Hazleton and has been found to be acceptable by DPR (see -271:126241 under combined rat), thus filling the chronic rodent data gap. A package from the interim sacrifice of this study (-246:112037) and unaudited histopathological findings from the terminal sacrifice (-261:119579) have also been submitted. Kellner, 12/20/93.

## DOG CHRONIC

\*\* 169, 056429 "One-year Oral Toxicity Study in Beagle Dogs with Carbaryl Technical" (Hazleton (VA), 3/18/87) Technical carbaryl, 99% pure, at 1250, 400, 125, or 0 ppm in the feed (about 34, 11, or 3.6 mg/kg/day) to 6/sex/level for 1 year; cholinesterase inhibition >25% at 1250 and 400 ppm, ChE NOEL = 125 ppm; neutrophilia, slightly increased inorganic phosphorus, and decreased serum albumin at 1250 ppm, not regarded to be adverse effects by reviewer, NOEL = 400 ppm; no clinical signs or organ toxicity, no adverse effects, toxicologic NOAEL = 1250 ppm (HDT). COMPLETE and ACCEPTABLE. F. Martz, 5/19/87.

EPA One-liner: No one-liner on file.

169-099 000718 "Chronic Toxicity of SEVIN for Dogs" (Mellon Institute, report #21-89, 10/1/58) Technical carbaryl was given by oral capsule at 7.2, 1.8, 0.45, or 0 mg/kg/day

(approximately equivalent to 400, 100, 25, or 0 ppm in the feed) 5 days/week for 1 year to 3-4 Cocker or Basenji hybrids/level; "cloudy swelling of the convoluted and loop [kidney] tubules; sudanophilic dust in the glomeruli..." at 7.2 mg/kg, not regarded by lab to be degenerative change, significance questionable. No other effects, major deficiencies, insufficient information.

UNACCEPTABLE and not upgradeable. J. Schreider, 5/10/85.

EPA One-liner: Systemic NOEL = 1.8 mg/kg, LEL = 7.2 mg/kg (diffuse cloudy swelling of proximal convoluted tubule). Core grade: supplementary.

154, Tab C, Section III, pp 3-4; Rebuttal to #000718 above, has no useful information on which to upgrade Mellon Institute study #21-89. Moot because repeat study (#056429 above) was accepted. F. Martz, 5/19/87 (no worksheet).

#### SUBCHRONIC, DOG

169-239 98146 ASubchronic Toxicity Study in Dogs with Carbaryl Technical® N. N. Hamada; Hazleton Laboratories America, Inc., Vienna, Virginia; Report # HLA 656-152; 8/5/91 [completed 3/28/91] Carbaryl Technical (99.3%, Lot # 87191); 6 dogs/sex/dose; 0, 20, 45, 125 ppm in the diet; observations: No mortalities due to test article were observed. No significant changes in bodyweight gain, total food consumption, food utilization, clinical observations, ophthalmic changes, or gross pathological changes considered treatment related were observed at any treatment level. Statistically significant decreases in plasma cholinesterase were seen in the 20, and 125 ppm males during Week 2 but were considered incidental. No significant inhibition of erythrocyte or brain cholinesterase levels were seen. NOEL (M/F) >125 ppm (M: 3.83 mg/kg/day, F: 4.11 mg/kg/day; based on no treatment related effects at high dose treatment); **Supplemental** (length of treatment, limited parameters measured, no histopathology, dose selection not justified: too low) (Miller, 1/21/98)

#### COMBINED RAT

\*\* **271 126241** Hamada, N. "Combined Chronic Toxicity and Oncogenicity Study with Carbaryl Technical in Sprague-Dawley Rats" (Hazleton Washington, Inc. (HWA), HWA Study No. 656-139, 9/7/93). Carbaryl technical (lot #12-CNG-32, purity 99%) was administered in the feed at concentrations of 0, 250, 1500, and 7500 ppm to 90 Sprague-Dawley rats/sex/group (control and high-dose) and 80 rats/sex/group (low- and mid-dose) for 104 weeks. Ten animals/sex/group were sacrificed for clinical pathology evaluation after 26, 52, 78 and 104 weeks; an additional 10/sex (control and 7500 ppm) were sacrificed at week 57 after receiving basal diet from week 53-57 (recovery groups). Body weights and food consumption were significantly lower in high-dose rats during most of the study and in 1500 ppm females at weeks 53 and 105. **Cholinesterase (ChE) NOEL = 250 ppm** (significant ChE inhibition at the mid- and high dose for erythrocyte and brain ChE and at the high dose for plasma ChE). Nonneoplastic findings: pigment, hyperplasia and eosinophilic foci (liver), foamy macrophages and pneumonitis (lung), vacuolization (pancreas), transitional cell hyperplasia (kidney and urinary bladder), follicular cell hypertrophy (thyroid), nerve degeneration (sciatic nerve/skeletal muscle), decreased leukocytes, unilateral and bilateral cataracts. **Systemic (female) NOEL = 250 ppm** (male weight effects at all dose levels). **Possible Adverse Effects:** neoplastic lesions at the high dose level in the urinary bladder (papilloma and carcinoma), kidney (single transitional cell carcinoma in males), liver (adenoma and foci) and thyroid (adenoma and a single carcinoma). ACCEPTABLE. Kellner and Gee, 12/20/93.

169-246 112037, "Combined Chronic Toxicity and Oncogenicity Study with Carbaryl Technical in Sprague-Dawley Rats" (52-Week Interim Report with 4-Week Recovery), (N. Nicki Hamada,

Hazleton Washington, Inc., Vienna, VA., Report #656-139, 12 December 1991). Sevin Technical (Carbaryl), 99.6% purity was used. This is a 52-week interim report (including a 4-week recovery period) for a 104 week study. The test compound was administered in the diet for 52 weeks at 0 (Purina<sup>7</sup> Certified Rodent Chow<sup>7</sup> # 5002), 250, 1500 or 7500 ppm with 80 (low and mid-dose) or 90 (control and high dose) CrI:CD BR rats per sex per group. Ten (10) per sex per group were necropsied at week 53. Additionally, following 52 weeks of treatment, 10 per sex each from the control and high dose groups were designated recovery animals and were placed on the basal diet for 4 weeks. These rats were sacrificed and necropsied at week 57. Reduced body weights were noted throughout the study at 1500 (females, 3% to 7% reduction) and 7500 (both sexes, 15% to 38% reduction) ppm. Increased relative (to terminal body weight) liver and kidney weight ratios were indicated for both sexes at 1500 and 7500 ppm. Hepatocellular intracytoplasmic hyaline inclusions were noted in 1 and 4 high dose males respectively at the unscheduled and interim (week 53) sacrifices. Histopathology of recovery animals (week 57 sacrifice) showed the absence of this finding, suggesting reversibility. **Adverse effects are not indicated.** Possible Chronic NOEL = 250 ppm (bodyweight reduction). ChE NOEL = 250 ppm (based on plasma, RBC and brain ChE inhibition at 1500 and 7500 ppm). **Unacceptable**, this 52-week interim report does not satisfy chronic data requirements in the rat for a food-use active ingredient. It is considered supplemental information, pending receipt of the final report. (H. Green, 1/15/92, and Gee, 1/23/92)

Note: Final report has been submitted and is acceptable; see 169 -271:126241.

**169-261 119579** [Addendum to -246:112037] Hamada, N. "Chronic Toxicity/ Oncogenicity Study with Carbaryl Technical in Rats Preliminary Data" (HWA Study No. 656-139, 11/3/92). Carbaryl technical was administered in the feed to Sprague-Dawley Rats at 0, 250, 1500 or 7500 ppm; this submission concerns preliminary unaudited neoplastic findings from terminally sacrificed rats and intercurrent deaths from Hazleton study #656-139. **Possible Adverse Effects:** Increased incidence of bladder (males and females), thyroid (males) and hepatocellular (females) neoplasia. Increased sciatic nerve and skeletal muscle degeneration in the high-dose group. Kellner and Gee, 8/31/93.

#### RAT ONCOGENICITY

Also See Combined Rat.

EPA One-liner: Rat Oncogenicity study on file (Carpenter et al., 1961, J. Agriculture and Food Chemistry, 9:30-39.); Core Supplementary.

#### MOUSE ONCOGENICITY

**\*\* 267 123769** Hamada, N. "Oncogenicity Study with Carbaryl Technical in CD-1<sup>7</sup> Mice" (Hazleton Washington, Inc. (HWA), HWA Study No. 656-138, 5/20/93). Carbaryl technical (lot #87191, purity 99.3%) was administered in the feed at concentrations of 0, 100, 1000 and 8000 ppm to 80 CD-1<sup>7</sup> mice/sex/group for 104 weeks. Ten animals/sex/group were sacrificed at interim (week 52). Non-neoplastic findings included increased incidence of intracytoplasmic (protein-like) droplets in the superficial transitional epithelium of the urinary bladder and increased hematopoiesis and pigment in the spleen (high-dose). High-dose mice appeared unthrifty (hunched, languid, thin, urine stains, rough coat and opaque eyes) and showed reduced body weight (18%) and food consumption (22%); lung and ovary weight were reduced and liver weight was elevated for the high dose groups; **Systemic NOEL = 100 ppm** (from effects seen in the urinary bladder). Cholinesterase activity (RBC-CHE and BR-CHE) showed significant decreases in the mid- and high-dose groups; **ChE NOEL = 100 ppm.** **Possible adverse effects:** Increased

hemangioma/hemangiosarcoma in all male dose groups and high-dose females; increased renal tubular cell adenoma and carcinoma in high-dose males and hepatocellular adenoma and carcinoma in high-dose females. Unilateral or bilateral posterior lens cataracts at high-dose. ACCEPTABLE. (Kishiyama, Kellner and Gee, 8/23/93).

**254 116336** [Addendum to -267:123769] Hamada, N. "Oncogenicity Study with Carbaryl Technical in Mice Preliminary Data" (Hazleton Washington, Inc., HWA Study No. 656-138, 7/21/92). Carbaryl technical, purity 99.3%, was administered in the feed at levels of 100, 1000 and 8000 ppm to 80 CD-1<sup>7</sup> mice/sex/group for 104 weeks; this submission reports preliminary neoplastic findings from terminally sacrificed mice and intercurrent deaths. **Possible Adverse Effects:** There were increased incidences of renal (high-dose males), hepatocellular (high-dose females), and vascular (males and females) neoplasia. Also reported was increased incidence of unilateral and bilateral cataracts in high-dose male and female mice. Supplemental Data. (Kellner and Gee, 8/6/93.)

169-247 112020 Partial duplicate of -267:123769. Contains data and analysis up to and including the 52-Week interim sacrifice. No worksheet. (Kellner, 9/7/93.)

099 000717 (with rebuttal and supplemental information in -154 and -161, 050437); "Results of Eighty Weeks of Inclusion of SEVIN in the Diet of Mice;" (Mellon Institute, report #26-53, 6/11/63) Technical carbaryl, 99.8% pure, in the feed at 400, 100, or 0 ppm to CD-1 mice, 48/sex/level for 80 weeks; approx. 50% mortality at 80 weeks, all groups, 2 of these autolyzed or cannibalized; 12/sex/level sacrificed at 80 weeks with no explanation of the survivors' fates; latter found only in supplemental information in #050437; no onco effects, but study generated little useful information. UNACCEPTABLE and not upgradeable. J. Schreider, 5/10/85 and F. Martz, 8/7/87.

EPA One-liner: Negative - dietary at 400 ppm (HDT)/day/2 yr. Core grade: supplementary.

169-154, Tab C, Section V, pg. 5: Rebuttal of #000717 above. Study can not be upgraded. Twelve/sex/level were interim sacrificed at 80 weeks and the study terminated at 2 years. Results of the terminal sacrifice are not given in the report. Approximately 50% of the mice died by 80 weeks, and one-half of these lost to autolysis and/or cannibalism; only 2-10 mice/level examined from interim sacrifice through termination; the tissue inventory is incomplete. Based on these considerations, the study is not upgradeable and the rebuttal will not be discussed further. F. Martz, 8/7/87.

169-161, 050437: Supplemental information to #000717 above, having the following:

Tab A: Copy of laboratory notebook 806. Individually lists by animal number, the calendar date and fate, age at fate, clinical observations, and gross necropsy observations. Note that this provides the first indication that the study actually went beyond 80 weeks. The report stated that 12/sex/level were sacrificed at 80 weeks with no explanation of the survivors' disposition.

Tab B: Copy of laboratory notebook 807. Contains diet room records showing amounts of carbaryl and feed used for each batch of feed mix.

Tab C: Consultant pathologist's second opinion of liver findings. No new effects noted. The slight increase in hepatocellular nuclear polyploidy noted originally at 80 weeks was rediagnosed as being "...present in the livers of all mice examined..." There was no change in the hepatocellular tumor incidence.

Tab D: Pathology report from 80 week sacrifice through termination.

Tab E: Pathology report from first death through 80 week sacrifice.

F. Martz, 8/7/87.

## MOUSE SUBCUTANEOUS ONCOGENICITY

169-023, 038178 (with rebuttal and additional information in -154 and -160, 50436); "Mammalian Toxicity of 1-Naphthyl-N-methylcarbamate (SEVIN Insecticide)" Mellon Institute, in J. Agr. Food Chem., 9:30-39 (1961); technical carbaryl in 0.25% agar by subcutaneous injection once weekly to 3 month old A/J or C3H males, 10 or 0 mg/mouse, 30/level, and 30 untreated controls, for 5 months with gross examination for lung masses at 8 months of age. UNACCEPTABLE, contains no useful information. J. Schreider, 5/6/85 and F. Martz, 5/5/87.

EPA One-liner: Negative - subcutaneous of 5% (10 mg) agar dilution (HDT) once/wk/20 wk. Core grade: supplementary.

169-154, Tab C, Section IV, pg. 5; Rebuttal of #038178 above. Study cannot be upgraded and rebuttal will not be further addressed. No status change. F. Martz, 5/5/87.

169-160, 050436; Copies of 4 laboratory notebook pages for #038178 above.

## RAT REPRODUCTION

\*\* 169 - 410 182115 Tyl, R. W., C. B. Myers and M. C. Marr " Two-generation reproductive toxicity evaluation of Carbaryl (RPA007744) administered in the feed to CD® (Sprague-Dawley) rats." (Research Triangle Institute, RTI 65C-07407-400, 5/24/2001) Technical grade carbaryl, 99.1%, was fed in the diet at 0, 75, 300 or 1500 ppm to 30/sex/group CD® Sprague Dawley rats for 1 litter per generation, two generations. At 1500 ppm, there were decreased body weight and food consumption in F0 and F1 parental animals with smaller effects at 300 ppm. In offspring, there were lower body weight, delay in vaginal opening and preputial separation (measured in F1 pups only), increased mortality in F1 and F2 pups at 1500 ppm with an increase in mortality in F2 pups at 300 ppm during lactation, especially pnd 0 - 4 (survival index of 98.3% for controls, 92.0% at 300 ppm - not statistically significant, and 88.9% at 1500 ppm - also not significant). Parental systemic NOEL = 75 ppm; reproductive NOEL = 1500 ppm (no effects); pup NOEL = 75 ppm. No specific adverse reproductive effects. ACCEPTABLE. (Gee, 1/7/02).

169 - 388 170645 ACarbaryl reproductive toxicity: Assessment of data adequacy for hazard assessment and evaluation of potential for increased susceptibility to the young@ (J. P. Rieth, Rhone-Poulenc Ag Company, report no JPR0199, May 20, 1999) The document is an assessment of the results of reproductive and developmental studies in view of FQPA and the need for an additional 10X safety factor and addressed to US EPA. The reproduction studies completed in 1966 and 1972 were discussed and a statement was made that a new reproduction study is in progress and due in December, 2000. SUPPLEMENTAL. (Gee, 9/10/99)

169 - 099 000716; "Results of a Three Generation Reproduction Study on Rats Fed SEVIN in Their Diets;" Mellon Institute report #28-53, 4/20/65; technical grade carbaryl, 99.8% pure, in the feed at 10, 2.5, or 0 mg/kg/day to 12-20 females/level, males unspecified, (F<sub>2a</sub>-->F<sub>3b</sub> for teratology portion); no reproductive effects, but no MTD; UNACCEPTABLE because of numerous deficiencies. J. Schreider, 5/10/85 and F. Martz, 8/6/87.

EPA One-liner: Reproductive, fetotoxic, and maternal NOEL=10 mg/kg (HDT). Core grade: minimum.

169 - 130 037909; Exact duplicate of #000716 above. F. Martz, 8/7/87.

154, Tab C, Section VI, pgs. 6-7, Rebuttal of #000716 above. Basically, an explanation of the study design in comparison to a FIFRA guideline study. My response is to quote the registrant's own rebuttal of the teratology portion of this study given in Section VII: "The value of this study will not be discussed in detail as the dosage levels used...were so much lower

than those used in a subsequent study." F. Martz, 8/6/87 (no worksheet).

162, 050438; Additional data included with rebuttal for #000716 above, consisting of photocopies of laboratory notebooks 911, 914, 945, and 951 as well as typed text and tables:

Tab A: Contains the "Diet Room Record" documenting the amounts of carbaryl and feed used for diet preparation;

Tab B: Individual body weights of F<sub>0</sub>, F<sub>1a</sub>, and F<sub>1b</sub>, and litter records for the F<sub>0</sub> and F<sub>1a</sub> rats;

Tab C: Body weights and mating records of the F<sub>2</sub> generation;

Tab D: Litter records for pups of the F<sub>2</sub> females;

Tabs E, F, and G: Pathology summaries and raw data for fetuses, weanlings, and 90 day old individuals from the F<sub>3</sub> offspring.

Additional data can not upgrade study. F. Martz, 5/19/87.

169-099 000712 (with rebuttal and additional data in -154, -165, 050441, and -166, 050442, 050955 & 56) "Comparative Study of Dietary Inclusion versus Stomach Intubation on Three-Generations of Reproduction, on Teratology and on Mutagenesis" (Mellon Institute, report #35-65, 8/31/72) Technical carbaryl, 99.6% pure, in feed at 200, 100, 25, 7, or 0 mg/kg/day; by gavage in corn oil at 100, 25, 7, 3, or 0 mg/kg/day; in feed containing corn oil at 100 or 0 mg/kg/day; 5 days/week (m->f); limited->complete histopathology on P<sub>0</sub> and F<sub>3a</sub> at 21 and 90 days old;

FEEDING RESULTS: MATERNAL - reduced weight gain at 200 mg/kg; NOEL = 100 mg/kg maternal, 200 mg/kg repro;

FEEDING/CORN OIL RESULTS: no effects at 100 mg/kg;

GAVAGE RESULTS: MATERNAL - tremors, mortality, and reduced weight gain at 100 mg/kg;

REPRO - decreased litter size at 100 mg/kg; NOEL = 25 mg/kg maternal and repro.

PROBLEMS: excessive postnatal mortality days 4-21 potentially hiding subtle effects, makes otherwise upgradeable study UNACCEPTABLE. J. Schreider, 5/13/85 and F. Martz, 8/7/87.

EPA One-liner for gavage: Reproductive NOEL = 25 mg/kg, fetotoxic LEL = 100 mg/kg (decreased "viable" fetuses), maternal LEL = 100 mg/kg (HDT; decreased weight gain, cholinergic signs, mortality). Core grade: Minimum.

EPA One-liner for feeding: Reproductive and fetotoxic NOEL = 200 mg/kg (HDT), maternal LEL = 200 mg/kg (decreased weight gain). Core grade: minimum.

169 - 130 037913: Exact duplicate of #000712 above.

169 - 154, Tab C, Section X, pgs. 10-11, Rebuttal of #000712 above. Specific comments are as follows:

A. Rebuttal: "A single daily dose intubation procedure is not considered by the authors to be a proper model for human exposure to pesticide residues in the diet." This concerns our criticism that carbaryl was administered by feed rather than gavage.

Response: We disagree. Humans may consume a carbaryl-laden meal in 10 minutes, whereas rats nibble their feed continuously albeit mostly with the first several hours of darkness.

B. Rebuttal: "Furthermore, the previous...studies using dietary inclusion ...demonstrated no reproductive or teratogenic effects."

Response: Dose levels (25 mg/kg HDT) were insufficient.

C. Rebuttal: "...the purpose of this study was [to compare]...the potential effect on reproduction in rats following daily dietary inclusion or gastric intubation. To attempt to compare the procedure used to the current FIFRA guidelines is inappropriate."

Response: We agree. Were it not for excessive postnatal mortality in particular, the study could be acceptable to fill the data gap.

D. Rebuttal: "The results of this study were, and are, very significant. Daily gastric intubation of

carbaryl resulted in maternal cholinesterase inhibition and mortality, as well as some effect on reproduction but the appropriate potential hazard route of administration, dietary inclusion, was without significant deleterious effect."

Response: We disagree that dietary inclusion is the most appropriate route of administration for reasons stated above.

E. Comment: The respondent seems to have missed the overwhelming significance of this study: the complete absence of teratogenicity with only minimal fetotoxicity or reproductive toxicity within the parameters covered at a gavage-administered dose level clearly producing significant maternal toxicity. That alone supports the relative "safety" of carbaryl to the developing organism. F. Martz, 8/6/87.

169 - 165, 050441 Additional data submitted with rebuttal for rat reproduction study with teratology and dominant lethal components (Mellon report #35-65, CDFA #169-099, #000712 and 027204), consisting of photocopies of laboratory notebooks;

Tab A: Individual body weights of  $F_0$  rats and identification of male-female mating pairs for  $F_{1a}$ ,  $F_{1b}$ , and  $F_{1c}$  offspring;

Tab B: "Diet Room Record" documenting usage of carbaryl and feed for diet preparation from start to 8/9/71, continued in Tab J;

Tab C: Individual body weights of oral gavage  $F_0$  parents and  $F_{1a}$  offspring from weaning through gestation of  $F_{2a}$ , and clinical observations.

Tab D: Contains body weight data for what appears to be a 4 week pilot study otherwise unidentified;

Tab E: Litter records for  $F_0$  matings;

Tab F: Individual body weights and mating-pair records for feed-treated  $F_{1a}$ ;

Tab G: Contains  $F_{1a}$  body weight information continued from Tab C, and  $F_{2a}$  body weights;

Tab H: Litter records for  $F_{1a}$  matings;

Tab I: Body weight records for  $F_{2a}$  rats from weaning through gestation of  $F_{3a}$  offspring;

Tab J: Contains diet room records continued from notebook in Tab B. F. Martz, 5/11/87.

169 - 166 Additional data for rat reproduction study with teratology and dominant lethal portions (Mellon report #35-65, CDFA #169-099, 000712 and 027204), consisting of photocopies of laboratory notebooks or typed reports;

Record # 050955:

Tab A contains litter records for  $F_{2a}$  dams which delivered, consisting of birth dates, individual pup weights and the number of live or dead pups in the  $F_{3a}$  generation;

Tab B contains similar litter records for  $F_1$  dams which delivered; Tab C contains individual body weight records for the gavage-treated  $F_{3a}$  groups;

Tab D contains similar information for feed-treated  $F_{3a}$  groups;

Record # 050442:

Tab E contains mating records for  $F_{2a}$  parents to produce the  $F_{3b}$  for the teratology portion of study;

Tab F contains individual  $F_{2a}$  dam sacrifice records for teratology portion of study, consisting of sacrifice calendar dates, the number of live or dead pups or resorption sites, the number of pups with gross anomalies and descriptions of observed anomalies, and litter weights;

Tab G contains a pathology report for an unidentified 1 month rat study at 150, 75, or 0 mg/kg/day via the feed;

Tab H contains pathology report for the sacrificed  $F_{3a}$  rats from the feed-treated groups, continued in Tab M for gavage-treated groups;

Tab I contains pathology report dated 3/21/72 for unidentified rat study using dietary dose levels

of 200 or 0 mg/kg/day;

Tab J contains pathology report also dated 3/21/72 for unidentified rat study using oral gavage dose levels of 100 or 0 mg/kg;

Tab K contains pathology report dated 2/22/72 for teratology portion of reproduction study, with tabulation of skeletal and visceral observations;

Record # 050956:

Tab L contains report of uterine observations from dominant-lethal portion of reproduction study;

Tab M is a continuation of material in Tab H, and contains a pathology report dated 6/23/72 for the sacrificed F<sub>3a</sub> pups from the gavage-treated groups;

Tab N contains duplicate pathology records for F<sub>3a</sub> pups sacrificed on day 21 as well as records for F<sub>3a</sub> rats sacrificed at 90 days of age;

Tab O contains pathology report dated 8/26/72 for F<sub>3a</sub> rats sacrificed at 90 days of age, appears to be duplicate of some material in Tab N.

F. Martz, 5/19/87.

**179 059543** "The Effect of Carbaryl (Sevin) on Reproduction of the Rat and the Gerbil." (Food and Drug Administration, Division of Pesticide Chemistry and Toxicology, DC, publication in Toxicol. Appl. Pharmacol. 19: 202-216 (1971), accepted 9/4/70, T. Collins et al.) Technical carbaryl, 99%; fed in the diet to Osborne-Mendel rats at 0, 2000, 5000 or 10,000 ppm, 20/sex/group, three generations, two litters per generation or to Mongolian gerbils at 0, 2000, 4000, 6000 or 10,000 ppm, three generations, two litters; NOEL for reproductive effects < 2000 ppm (LDT) in both species with reduced weaning weights at all doses, decreased viability, survival, weaning indices at 5000 and 10,000 ppm in the rat with no animals at 10,000 for the second F1 mating or the F2 matings; no abnormalities reported; parental NOEL in the rat appeared to be 5000 ppm from the text; effects similar in the gerbil; no microscopic pathology included in the report; insufficient information to evaluate parental effects; unacceptable, not upgradeable (no reproductive NOEL - all doses too high). Gee, 9/30/88.

Previous summary: Although no study alone is adequate, the collective data provide sufficient information. The 1971 study indicated a possible adverse effect on reproduction at a dose not obviously toxic to the parental animals from the report. The publication by Collins et al., however, contains insufficient information for independent assessment of the parental toxicity. The later (1972) study, Record # 000712 and supplements, demonstrated a reproduction NOEL of 200 mg/kg in the feeding portion and a maternal NOEL of 25 mg/kg with no adverse developmental effect. Excessive postnatal mortality was seen in all groups, including the control so it was not a clear treatment effect. Since this study is much more complete and establishes NOELs, the conclusion is that there is no adverse reproduction effect without parental effects. From the 1972 study, it is likely that cholinesterase was markedly inhibited in the parental animals in the study by Collins et al. The collective data fill the data gap. Gee, 10/25/88.

NOTE: Record No. 170645 in 169-388 contains a statement that a new reproduction study is in progress with a due date of December, 2000. Gee, 10/1/99. This study was submitted in 169 - 410, record no. 182115 - see 1-liner above. Gee, 1/7/02.

#### RAT TERATOLOGY

\*\* 169-383 166125 A Carbaryl: Developmental toxicology study in the rat by gavage.® (M. Repetto-Larsay, Study Director, Rhone-Poulenc Agro, Study SA 98070, October 21, 1998). Pregnant rats (CrI:CD(SD)BR), 25 per group, were given carbaryl (lot 208 115 110, 99%), at doses of 0 (0.5% methylcellulose 400), 1, 4 or 30 mg/kg/day by gavage, days 6 - 20 of gestation.

Fetuses were given an external examination and approximately half were examined for visceral changes and half for skeletal effects. At 30 mg/kg/day, 18/25 dams had increased salivation within 20 minutes of dosing, disappearing within 1 hour and observed primarily between days 14 to 20 of gestation. In addition, maternal body weight was reduced statistically significantly at 30 mg/kg and fetal body weight was also reduced at 30 mg/kg. Maternal NOEL = developmental NOEL = 4 mg/kg/day (body weights, clinical signs in dams). ACCEPTABLE. No adverse effect. (Gee, 2/22/99)

169 - 099 000716 (With rebuttal and additional information in -154 and -162, 50438): "Results of a Three Generation Reproduction Study on Rats fed SEVIN in Their Diets," teratology of F<sub>3b</sub>; Mellon Institute, report #28-53) 4/20/65; technical grade carbaryl, 99.8% pure, in the feed at 10, 2.5, or 0 mg/kg/day to 17-18 pregnant rats/level (F<sub>2a</sub> of reproduction study) from prior to mating to sacrifice day 18-21; no soft tissue exams; no developmental toxicity, but no maternal MTD. UNACCEPTABLE and not upgradeable. J. Schreider, 5/10/85 and F. Martz, 5/6/87.  
EPA One-liner: None in file.

169 - 154, Tab C, Section VII, pg. 8, Rebuttal of #000716 above: To quote: "The value of this study will not be discussed in detail as the dosage levels used...were so much lower than those used in a subsequent study." Agree. FMartz, 5/6/87.

169 - 162 050438 Additional data included with rebuttal for #000716 above, consisting of photocopies of laboratory notebooks 911, 914, 945, and 951 as well as typed text and tables:

Tab A: Contains the "Diet Room Record" documenting the amounts of carbaryl and feed used for diet preparation.

Tab B: Individual body weights of F<sub>0</sub>, F<sub>1a</sub>, and F<sub>1b</sub>, and litter records for the F<sub>0</sub> and F<sub>1a</sub> rats;

Tab C: Body weights and mating records of the F<sub>2</sub> generation ;Tab D: Litter records for pups of the F<sub>2</sub> females;

Tabs E, F, and G: Pathology summaries and raw data for fetuses, weanlings, and 90 day old individuals from the F<sub>3</sub> offspring. Additional data do not upgrade study although they indicate good documentation procedures. F. Martz, 5/19/87.

169 - 099 000715 ( With rebuttal and additional information in -154 and -163, 50439)  
"Evaluation of the Teratogenic Potential of Insecticide SEVIN in Rats;" Mellon Institute, report #29-49, 7/28/66; technical grade carbaryl, 99.7% pure, in the feed, adjusted to give 500, 100, 20, or 0 mg/kg/day to 3 groups, 12/level each, treated: (1) throughout pregnancy or until weaning, (2) gestation days 0-7, or (3) gestation days 7-15; one-half sacrificed days 19-21, other half allowed to deliver with termination 21 days postpartum; gross and skeletal exams only;  
MATERNAL: dose-related weight gain reduction, severest in group 1 (dosing throughout pregnancy);  
DEVELOPMENTAL: none - no fetotoxicity or skeletal malformations; POSTNATAL: reduced live litter size and postnatal survival at 500 mg/kg (not considered a teratogenic effect);  
MATERNAL NOEL = 20 mg/kg; FETOTOXIC NOEL = 100 mg/kg (based on reduced liveborn litter size); TERATOGENIC NOEL = 500 mg/kg (soft tissue exclusive). UNACCEPTABLE and not upgradeable. J. Schreider, 5/10/85 and F. Martz, 8/6/87.  
EPA One-liner: Teratogenic NOEL > 500 mg/kg (HDT), maternal LEL = 500 mg/kg (decreased weight gain), fetotoxic LEL = 500 mg/kg (mortality). Core grade: minimum.

169 - 130, 037910 Exact duplicate of #000715 above.

169 - 154, Tab C, Section VIII, pg. 8, Rebuttal of 29-49 above: Points are addressed as listed:

A. Rebuttal: "This design is more informative than [sic] the cook-book one in the guidelines..."

Response: We agree that the study design would provide more useful information overall than the standard Segment II type of teratology study, if all relevant parameters were covered, which they weren't.

B. Rebuttal: "It is notable that the dosage levels are remarkable and appropriate..."

Response: We agree. That the high dose level was a MTD is documented by the severely reduced body weight gain during gestation in that group.

C. Rebuttal: "The frequency of weighings and food consumption measurements, and these results for individual animals and dosage groups, may be found in the supplied Mellon Institute notebook 984 and 987."

Response: Located in -063, 50439.

D. Rebuttal: "The reviewer remarked: 'Sex and weight of fetuses not recorded.' The results are summarized...in Table 29-88..."

Response: Table gives body weight of pups at weaning only. The fetal weights recorded at hysterectomy are still unaccounted for.

Comment: There is no evidence that soft tissue examinations were done. Therefore, the potential to cause visceral malformations remains unanswered by the data collected in this study.

Conclusion: The study is incomplete, unacceptable, and not upgradeable. F. Martz, 5/6/87.

169 - 163 050439 Additional data for rat teratology study #29-49, (CDFA #169-099, 715), consisting of photocopies of laboratory notebooks 911, 984, and 987:

Tab A contains "Diet Room Records" documenting the amounts of carbaryl and feed used in preparing diet blends.

Tab B contains individual female body weight values.

Tab C contains uterine examination observations of dams killed on day 20, and litter records on dams allowed to deliver and wean their offspring. Records consist of total pups in utero and dead or resorbed pups, anomalous observations, the dates of sacrifice or weaning, the number of pups born, on day 4 and 21, the individual pup weights according to sex on day 21, and any abnormalities.

While this volume contains good documentation of experimental conduct, it does not upgrade the report, mainly due to lack of feed analysis and soft tissue examinations. F. Martz, 5/12/87.

\*\* 169 - 099 027204 (With rebuttal and additional information in -154 and -166, 50442)

"Comparative Study of Dietary Inclusion versus Stomach Intubation on Three-Generations of Reproduction, on Teratology and on Mutagenesis;" Mellon Institute, report #35-65, 8/31/72; technical carbaryl, 99.6% pure; in feed at 200, 100, 25, 7, or 0 mg/kg/day; by gavage in corn oil at 100, 25, 7, 3, or 0 mg/kg/day; in feed with corn oil equivalent at 100 or 0 mg/kg/day; to 6 month F<sub>2a</sub> males and females 5 days/week (M->F) before and during mating/gestation; F<sub>3b</sub> offspring examined;

FEEDING RESULTS: MATERNAL - decreased weight gain at 200 mg/kg, FETAL - incomplete ossification at 200 mg/kg; NOEL = 100 mg/kg maternal and fetal;

FEEDING/CORN OIL RESULTS: no effects at 100 mg/kg;

GAVAGE RESULTS: MATERNAL - cholinergic signs, mortality and reduced weight gain at 100 mg/kg, FETAL - reduced live litter size, more litters with resorptions, and incomplete ossification at 100 mg/kg; NOEL = 25 mg/kg maternal and fetal. Originally unacceptable (J. Schreider, 5/20/85) but upgraded to ACCEPTABLE (with major deviations). F. Martz, 5/87.

EPA One-liner for gavage: Teratogenic NOEL > 100 mg/kg (HDT), maternal LEL = 100 mg/kg (decreased weight gain, cholinergic signs, mortality), fetotoxic NOEL = 100 mg/kg (decreased live fetuses). Core grade: minimum.

EPA One-liner for feeding: Teratogenic NOEL > 200 mg/kg (HDT), maternal LEL = 200 mg/kg (decreased weight gain), fetotoxic NOEL > 200 mg/kg. Core grade: minimum.

154, Tab C, Section XI, pg. 11, Rebuttal of above study. Registrant's rebuttal and CDFA's response is similar to that given in "REPRODUCTION RAT, 35-65" below. We agree with rebuttal. In spite of major deviations from guidelines, the data appear to have been gathered in a manner scientifically valid and with good documentation. Total "weight of evidence" supports the absence of teratogenic potential. In my opinion, no new significant information would be gained from a study conducted according to current guidelines. Therefore, the teratology data gap is filled. F. Martz, 5/6/87.

166, 050422; Additional data for #027204 above; see -166 entry under "REPRODUCTION RAT (Mellon Report #35-65)."

169 - 131 to 133, 037925-27 "Teratology Study - SEVIN, Vitamin A, Aspirin and Malathion;" Litton, 6/23/72; technical carbaryl, 99.6% pure, in the feed at 7000, 4000 or 0 ppm (approximately 375 or 200 mg/kg) to timed pregnant Sprague-Dawley females (Flow Labs; plug day=0), 20/level, days 6-15 with sacrifice on day 18, 1/3 fetuses visceral, remaining skeletal; no developmental toxicity, maternal weight gain can not be assessed from data presented, but data "...do not appear to show any evidence of maternal toxicity;" NOEL>7000 ppm (approximately 375 mg/kg). F. Martz, 12/11/85 and 8/7/87.

EPA One-liner: NOEL = 375 mg/kg (HDT). Core grade: supplementary.

#### RABBIT TERATOLOGY

\*\* 169-389 170646 ADevelopmental toxicity evaluation (with cholinesterase assessment) of carbaryl administered by gavage to New Zealand White rabbits® (R. W. Tyl, M. C. Marr and C. B. Myers, Research Triangle Institute, RTI No. 65C-7297-200/100, 6/3/99) New Zealand White rabbits, 22/dose group, were given carbaryl (batch 208115110, 99% purity) by gavage at 0 (0.5% aqueous methylcellulose), 5, 50 or 150 mg/kg body weight/day on days 6 through 29 of gestation. Animals were sacrificed on gestation day 30. Dose selection was based on a range-finding study with 100 mg/kg as the high dose. Plasma cholinesterase was inhibited to 41% of control and RBC cholinesterase was 80.1% of control (not statistically significant) at 100 mg/kg. In the definitive study, body weight gain was reduced at 150 mg/kg, being 47% of control. Total body weight, however, was not significantly lower. Plasma cholinesterase was 46% and 32% of control at 50 and 150 mg/kg/day, respectively. Red blood cell cholinesterase was 81% and 73% of control at these doses. These values were statistically significant. At 150 mg/kg, fetal body weight was reduced, being 90% of control. There were no other developmental affects reported as related to treatment by the authors. There were two fetuses in two litters with agenesis of the gall bladder(10%, p = 0.27 by Fisher-s Exact) and 4 fetuses from three additional litters reported as having gall bladders Ahalf normal size.® These incidences were compared with 0/18 for the concurrent controls. The historical control incidence for agenesis of the gall bladder included in the report indicated 1/187 litters (0.53%). Maternal NOEL = 5 mg/kg (cholinesterase inhibition). Developmental NOEL = 50 mg/kg (reduced fetal body weight) No adverse effects. ACCEPTABLE. (Gee, 9/24/99)

Report not in CDFA file, but study by Robens (FDA), "Teratologic studies of carbaryl, diazinon, norea, disulfiram, and thiram in small laboratory animals," was published in Toxicol. Appl. Pharmacol. 15: 152-163 (1969).

EPA One-liner: Teratogenic, fetotoxic, and maternal NOEL all > 200 mg/kg by oral gavage (HDT). Core grade: minimum.

Report not in CDFA file, but study by Murray et al, "Teratogenic potential of carbaryl given rabbits and mice by gavage or by dietary inclusion," was published in Toxicol. Appl. Pharmacol. 51: 81-89 (1979).

EPA One-liner: Teratogenic, fetotoxic, and maternal NOEL al l > 200 mg/kg by oral gavage

(HDT). Core grade: minimum.

#### MOUSE TERATOLOGY

Report not in CDFA file, but study by Murray et al, "Teratogenic potential of carbaryl given rabbits and mice by gavage or by dietary inclusion," was published in Toxicol. Appl. Pharmacol. 51: 81-89 (1979).

EPA One-liner for gavage: Teratogenic and fetotoxic NOEL > 150 mg/kg (HDT), maternal LEL = 150 mg/kg (decreased weight gain, cholinergic signs). Core grade: minimum.

EPA One-liner for feeding: Teratogenic NOEL > 1166 mg/kg (HDT), fetotoxic LEL = 1166 mg/kg (decreased weight), maternal LEL = 1166 mg/kg (decreased weight gain). Core grade: minimum.

#### TERATOLOGY DOG

**169 - 099 000714** "Sevin - Safety Evaluation by Feeding to Female Beagles From Day One of Gestation Through Weaning of the Offspring" (Woodard Res. Corp., 1/22/69) "Sevin technical grade," 99.8% pure, in the feed at 12.5, 5.0, 2.0, or 0 mg/kg/day, gestation day 1 through weaning at 6 weeks of age; increased stillbirths at 12.5 and 5 mg/kg; decreased birth weights and reduced survival to weaning at 12.5 mg/kg; inconclusive treatment-related malformations. UNACCEPTABLE and not upgradeable because of numerous deficiencies. J. Schreider, 5/10/85 and F. Martz, 8/4/87

EPA One-liner: Teratogenic NOEL = 2 mg/kg (LDT), teratogenic LEL = 5 mg/kg - (umbilical hernia, cleft palate, gastrointestinal abnormalities), Maternal NOEL < 2 mg/kg - (dystocia). Core grade: supplementary.

130, 037911: Exact duplicate of #000714 above.

**No Record Number.** Smalley, H. E., J. M. Curtis and F. L. Earl "Teratogenic action of carbaryl in beagle dogs." Published in Toxicology and Applied Pharmacology 13: 392 - 403 (1968) (Division of Pharmacology and Toxicology, Food and Drug Administration, U. S. Department of Health, Education and Welfare) Technical grade carbaryl (lot 5072, 99.9%) was fed in the diet to beagle dogs at 0, 3.125, 6.25, 12.5, 25 or 50 mg/kg/day. Females were mated when in estrus with one male on day 1 and a second male on day 3. Dosing began on a Wednesday between day 3 and day 6 after mating. With the exception of 6 dogs, all were allowed to give birth and the pups weaned at 8 weeks. Following weaning, they were sacrificed and autopsied. The number of females per dose group varied between 16 for concurrent controls and 8 at the highest dose. There were no clinical signs or differences in body weight with treatment compared with the controls. Dams were also necropsied at week 8 postpartum. Although pup weights were similar at birth, weight gain was lower in all test groups (data by graph only). The percent conception ranged from 81% for controls to 37% for the 50 mg/kg/day group. The incidence of dystocia was increased in all treatment groups, being 3/group at 3.125, 6.25, 25 and 50 mg/kg and 5/18 at 12.5 mg/kg/day but with no clear dose response over the 16-fold difference in doses. The percent of pups born alive at 50 mg/kg was zero (0). The percent weaned was also decreased in the treatment groups but no cause of death was established. The litters with pups with abnormalities was increased with treatment above 3.125 mg/kg, being 0/13, 0/7, 1/7, 3/16, 3/6, and 1/2, control through high dose. The historical control value was 3/313. The authors state that the difference between 12.5 mg/kg and 25 mg/kg was not statistically significant. The percent of pups with abnormalities was 0, 0, 9, 18, 13 and 14% with increasing dose compared with a historical control value of 0.1%. The most serious effect was failure of the liver to develop. Also, a number of pups had openings in the ventral abdominal wall. Cholinesterase activity was not measured. **Possible adverse effects.** Maternal NOEL < 3.125 mg/kg/day based on dystocia incidence due to atonic

uterine musculature. Developmental NOEL = 3.125 mg/kg/day (litter and pup incidence of abnormalities). The study indicates maternal and developmental toxicity but has limitations in terms of interpretation due to the small group sizes and the lack of a dose response for dystocia in dams over a 16-fold range in dose. SUPPLEMENTAL. (Gee, 10/22/99).  
EPA One-liner: Teratogenic NOEL = 3.1 mg/kg (LDT), teratogenic LEL = 6.3 mg/kg (lack of tail, agenesis of external genitals, failure of pubis and ischium to develop, abdominal fissures, visceral agenesis), maternal NOEL < 3.1 mg/kg (dystocia). Core grade: Supplementary.

#### TERATOLOGY MONKEY

Report not in CDFA file, but an unpublished 1974 gavage study is listed with EPA One-liners: Teratogenic NOEL > 20 mg/kg (HDT), maternal NOEL > 20 mg/kg. Core grade: minimum.

#### TERATOLOGY GUINEA PIG

169 - 099 000713 (With rebuttal and additional information in -154 and -164, 50440); "Study of Guinea Pig Teratology of SEVIN fed in the Diet versus Stomach Intubation," report #34-81; Mellon Institute, 11/30/71; technical grade carbaryl, 99.6% pure, in the feed at 300, 200, 100, or 0 mg/kg/day, or by oral gavage in corn oil at 200, 100, 50, or 0 mg/kg/day, on single or multiple day "windows" from day 10 through 24 (plug day = 1), with sacrifice day 34-35; MATERNAL: reduced weight gain and death at 200 mg/kg gavage; FETAL: no malformations or clear evidence of fetotoxicity in spite of maternal toxicity. GAVAGE NOEL = 200 mg/kg for developmental, 100 mg/kg for maternal; FEEDING NOEL = 300 mg/kg for developmental and maternal. UNACCEPTABLE but has useful information. J. Schreider, 5/10/85 and F. Martz, 8/7/87.

EPA One-liner for gavage: Teratogenic NOEL 200 mg/kg (HDT), maternal LEL = 200 mg/kg (decreased weight gain, mortality), fetotoxic NOEL > 200 mg/kg.

EPA One-liner for feeding: Teratogenic NOEL > 300 mg/kg (HDT), maternal NOEL > 300 mg/kg, fetotoxic NOEL > 300 mg/kg.

Core grade for both: minimum.

169 - 154, Tab C, Section IX, pg. 9: Rebuttal of #713 above. Comments are as follows:

Rebuttal: "The purpose of this study was to determine the potential teratogenicity to guinea pigs by two routes of oral administration and at maternally lethal and sublethal concentrations" [in order to assess the results of Robens (1969) showing that 300 mg/kg administered to guinea pigs by capsule caused skeletal defects albeit with 38% maternal mortality]. "Note: It is inappropriate to compare the protocol design ["teratogenic window" dosing] of this study to the routine FIFRA teratology guidelines."

Response: This was an exploratory rather than "standard" protocol study, but the various periods of organogenesis were covered by sufficient animals when the study is taken as a whole. Moreover, no fetal effects were seen in the absence of maternal toxicity at oral gavage dose levels approaching the LD<sub>50</sub> established in a preliminary study for this strain of guinea pig. Considering that such treatment was more rigorous than dietary exposure, the absence of frank teratogenicity is noteworthy. Report by itself is still unacceptable, but rebuttal is accepted based on "weight of evidence." F. Martz, 5/8/87.

164, 050440; Additional data included with rebuttal for #713 above, consisting of photocopies of laboratory notebooks 1129 and 1138, as well as typed tables and reports:

Tab A: Contains the "Diet Room Record," documenting the amounts of carbaryl and feed used for diet preparation;

Tab B: Litter records consisting of the dams' sacrifice dates, the number of live or dead

fetuses, resorption sites, individual fetal weights according to sex, and a description of gross anomalies if present;

Tab C: Pathology report dated 10/15/71 consisting of gross and microscopic observations of the livers and kidneys from dams receiving the top dietary or gavage dose levels as well as the respective controls;

Tab D: Pathology report dated 9/3/71 consisting of skeletal examination findings;

Tab E: Pathology report dated 12/1/71 consisting of soft tissue examination findings;

Tab F: Pathology raw data records.

(F. Martz, 5/19/87).

#### TERATOLOGY - GENERAL SUPPORTIVE INFORMATION

169 - 155, Tab B, no record #; Correspondence dated 5/13/85 from EPA (Douglas D. Camp) to Union Carbide (J.S. Lovell) concerning carbaryl registration standard. Among several points raised, EPA maintained its request for repeat of the 1958 chronic dog study unacceptable due to major deficiencies, and extended the due date to 5/87 [Note that the new report was completed 3/18/87, received by Medical Toxicology 5/11/87, and reviewed and accepted 5/12/87]. EPA rescinded its request for a repeat dog teratology study (listed in the Registration Standard), stating that "The agency has concluded that carbaryl would not constitute a potential teratogenic hazard to humans based on the overall weight of numerous (24) teratology studies that have been conducted. We also believe that the dog is not an appropriate model to perform a teratology study and relate it to humans." \*\*NOTE that EPA reconsidered this matter in 1986 and "concluded that it was needed" (Pesticide and Toxic Chemical News, 4/30/86).

169 - 155, 050430 An undated position paper from Drs. J.G. Wilson, A. Koestner, and C.H. Williams (recognized experts), evaluating the teratologic potential of carbaryl, with appropriate references. In their opinion, "On the basis of these animal studies, carbaryl could not be classified as a general teratogen." I agree. F. Martz, 5/87.

Regarding positive responses in dog studies at 5 mg/kg and above, they regard that "This seemingly unique response of the beagle dog to carbaryl may in part be explained by certain metabolic peculiarities of this species with respect to this compound. The pathways for metabolism of carbaryl differ somewhat among mammalian species, but the dog stands alone in conjugating carbaryl directly, being unable to liberate 1-naphthol or to hydroxylate the parent compound (Khera, 1976). The National Institute for Occupational Safety and Health (NIOSH) in an exhaustive study of the safety of carbaryl in the workplace (Criteria for a Recommended Standard for Carbaryl, 1976), has concluded that: 'Present studies show that the metabolism of carbaryl in the dog differs from that in humans, monkeys, rats, and guinea pigs so it is unwarranted now to extrapolate from dogs to humans regarding the teratogenic potential of carbaryl.'" They agree "...with NIOSH that it would be inappropriate to use data from the dog in [developmental] safety evaluations applicable to man." F. Martz, 5/12/87.

169 - 130, 037915-24; Exact duplicate of 50430 above.

169 - 155, 050431 A 1976 EPA review/position paper from Dr. Neil Chernoff regarding reproductive and teratogenic potential of carbaryl, with appropriate references. In his opinion, "I feel that with the exception of the dog, in cases where severe maternal toxicity has not been observed there have been no consistent adverse reproductive or fetotoxic effects induced by carbaryl. The positive effects seen in the dog must be evaluated in light of its reported unusual metabolism. In the other species where positive effects have been shown, these effects must be considered in terms of maternal toxicity induced by the treatment, and the extremely high dose

levels used. I feel that the use of such experiments which test for the maximum potential of a compound to induce effects is necessary to indicate types of effects to be looked for at lower dose levels (and such studies are regularly done in my laboratory). I do not feel that such studies should be afforded important consideration in the overall toxicological evaluation of safety for the continued use of carbaryl. I feel, therefore, that the evidence to date does not indicate that continued use of carbaryl would pose a reproductive or fetotoxic threat to man." Based on the current weight of evidence, I agree. F. Martz, 5/12/87.

See Summary of Toxicology Data dated September 14, 1987 prepared by F. Martz with Note: The conclusion of Dr. Martz was that the data gap for teratology studies in a second species was filled with a second review by J. Parker.

#### GENE MUTATION

EPA One liner: There are (at least) 18 gene mutation assays. Although most had deficiencies, REAG accepted them collectively to demonstrate weakly positive response (EPA-600/6-81-001, January, 1981). These 18 studies are not on file at CDFA for independent review. In March, 1990, CDFA did not consider the data gap as filled because of the incomplete data base on file compared with that of EPA. Subsequent communication with the registrant (see 169-206) indicated these studies were not available for submission. The data gap status has been changed to filled. Gee, 7/31/90.

\*\* 196 085660 "Mutagenicity Test on Carbaryl (Technical) in the Ames Salmonella/Microsome Reverse Mutation Assay." (Hazleton Laboratories America, Kensington, MD, HLA Study No. 10862-0-402, 9/6/89) Carbaryl technical, lot # 87191, 99.3% purity; tested with Salmonella typhimurium strains TA1535, TA1537, TA1538, TA98 and TA100, triplicate plates, two trials; with and without Aroclor 1254-induced male Sprague-Dawley rat liver activation; Trial 1: 0 (DMSO), 5, 10, 50, 100, 500, 1000 ug/plate ; Trial 2: 0 (DMSO), 10, 50, 100, 500, 1000, 2000 ug/plate. **No evidence of increase in reversion rate.** Acceptable. (Gee, 2/28/90)

\*\* 196 085658 "Mutagenicity Test on Carbaryl (Technical) in the CHO/HGPRT Forward Mutation Assay." (Hazleton Laboratories America, Kensington, MD, HLA No. 10862-0-435, 11/6/89) Carbaryl technical, lot 87191, 99.3% purity; tested with CHO-K1-BH<sub>4</sub> in vitro with and without Aroclor 1254-induced rat liver activation; single culture per concentration, 2 trials; without activation, trial 1: 0 (DMSO), 0.001, 0.01, 0.03, 0.05, 0.08, 0.1, 0.15, 0.2, 0.3 (T) mg/ml; trial 2: 0 (DMSO), 0.01, 0.05, 0.1, 0.15, 0.2, 0.25 (T), 0.3 (T) mg/ml; with activation, trial 1: 0 (DMSO), 0.01, 0.05, 0.08, 0.1, 0.15, 0.2, 0.3 (T) mg/ml; trial 2: only 1 concentration could be scored due to cytotoxicity with new lot of S9; trial 3: 0 (DMSO), 0.001, 0.005, 0.01, 0.02, 0.04, 0.06, 0.08, 0.1 (T), 0.13 (T); **no reproducible increase in forward mutations.** Acceptable. (Gee, 2/28/90)

200 090474 Revised report of 085658.

#### CHROMOSOMAL ABERRATION

169 - 099, 027202 (with rebuttal and additional data in -154, and -166, 050442, 050956); "Comparative Study of Dietary Inclusion versus Stomach Intubation on Three-Generations of Reproduction, on Teratology and on Mutagenesis," dominant lethal portion; Mellon Institute, report #35-65, 8/31/72; technical carbaryl, 99.6% pure in feed at 200, 100, 25, 7, or 0 mg/kg/day; by gavage in corn oil at 100, 25, 7, 3, or 0 mg/kg/day; in feed containing corn oil at 100 or 0 mg/kg/day; 5 days/week (m->f); F<sub>2a</sub> males withdrawn at 7 months old, mated weekly for 10 weeks:

FEEDING RESULTS: No dose-related or consistent differences, NOEL = 200 mg/kg;  
FEEDING/CORN OIL RESULTS: no effects at 100 mg/kg, NOEL = 100 mg/kg;  
GAVAGE RESULTS: Significant reduction in mean implants or viable fetuses at 100 mg/kg in week 8 mating only, 12.5 vs 14.0 control or 11.5 vs 14.0 control, respectively. Not regarded to be meaningful. NOEL = 100 mg/kg/day.  
Originally reviewed as unacceptable without useful data (J. Schreider); now is UPGRADEABLE with additional information. F. Martz, 8/20/87.  
EPA One-liner: None on file.

165 050441 Supplement to 027202.

166, 050442 & 050956; see "Reproduction Rat (Mellon report #35-65)" above for listing of entries.

169 - 179 059544 "UC 51762 - Inclusion in the Diet of Rats for Three Generations and Dominant Lethal Mutagenesis Studies." Supplemental to Record # 027202. (Carnegie-Mellon Institute, Report 42-65, 7/2/79) Positive control data with TEM given by i.p. injection to male Fischer 344 rats and mated with 1 female for each of three weekly periods. TEM caused increased resorptions in all three weeks. Supplemental data. No change in status of # 027202. Gee, 10/3/88.

\*\* **196 085657** "Mutagenicity Test on Carbaryl Technical: In an *in vitro* Cytogenetic Assay Measuring Chromosomal Aberration Frequencies in Chinese Hamster Ovary (CHO) Cells." (Hazleton Laboratories America, Kensington, MD, HLA Study no. 10862-0-437, 8/31/89) Carbaryl technical, Lot # 87191, 99.3%; tested with CHO-WBL cells *in vitro* for chromosomal aberrations; without S9, at 0 (negative and solvent), 7.5, 10, 25, 50 or 75 ug/ml, 17.5 hours incubation and 20-hour harvest, duplicate cultures; with Aroclor 1254-induced Sprague-Dawley rat liver S9 activation at 0 (negative and solvent), 150, 200, 250 or 300 ug/ml, duplicate cultures, 2 hour incubation and harvest at 20 and at 30 hours; harvest times based on a preliminary study with BrdUrd staining for determination of cell cycles in 27.5 hours total; no increase in aberrations without activation; **possible adverse effect with activation - increase in aberrations/cell, % cells with aberrations and % cells with >1 aberration at both harvest times.** Acceptable. (Gee, 2/27/90)

EPA One liner: EPA considers the following studies acceptable for filling the chromosome mutation data gap: Can. J. Genet. Cytol., 8:481-501, 1966.; Cytologia, 30:175-181, 1965; Cytologia, 33:334-337, 1968; Flora (Jena), 160:443-439, 1971; Archiv za Poljoprivedne Naake, 25:128-138, 1973. The studies cited by EPA above need to be submitted for independent review by CDFA. Gee, 3/90.

#### DNA DAMAGE/REPAIR

EPA One liner: There are 3 DNA repair assays (Mutation Research, 42:161-174, 1977; Mutation Research, 38:293-302, 1976; Mutation Research, 22:121-126, 1974) which collectively fill the data gap. These studies are not on file at CDFA and need to be submitted. Gee, 3/5/90.

\*\* 196 085659 "Mutagenicity Test on Carbaryl Technical in the *in vitro* Rat Primary Hepatocyte Unscheduled DNA Synthesis Assay." (Hazleton Laboratories America, Kensington, MD, HLA Study No. 10862-0-447, 11/22/89) Carbaryl technical, lot 87191, 99.3% purity; tested with primary rat hepatocytes from male Fischer 344 rats, two trials; trial 1: 0 (DMSO), 0.5, 1.0, 2.5, 5, 10 or 25 ug/ml; trial 2: 0 (DMSO), 5.0, 7.51, 10, 15, 20 or 25 ug/ml; scored 150 cells per concentration from triplicate coverslips; **no evidence of unscheduled DNA synthesis.** Acceptable. (Gee,

2/28/90)

#### NEUROTOXICITY, HEN

134, 037928 (with rebuttal and additional information in -154 and 156, 50432); "Comparison of the Demyelination Potential of SEVIN and Triorthocresyl Phosphate in Chickens, with Observations on the effects in Liver, Kidney, and gastrocnemius Muscle Tissue;" Mellon Institute, report #21-87, 9/15/58; no brain, spinal cord or sciatic nerve effects at 3 g/kg, subcutaneously, but results inconclusive because of weak TOCP effect also at 3 g/kg. F. Martz, 5/4 and 8/7/87 (no worksheet).

EPA One-liner: Negative at 2000 mg/kg (approximate LD<sub>50</sub>). Core grade: minimum.

154, Tab C, Section I, pg. 1, and 169-156, 50432, rebuttal to 169-023, no record#; Rebuttal not necessary because study is not required, inasmuch as carbamates have no documented neurotoxic potential such as that exhibited by organophosphates. F. Martz, 8/7/87 (no worksheet).

#### NEUROTOXICITY, DEVELOPMENTAL

169-384 166126 AA developmental neurotoxicity study of orally administered carbaryl, technical grade, in the rat (K. Robinson and B. Broxup, ClinTrials BioResearch Ltd., Quebec, Project 97391, 9/23/97). Sprague-Dawley CrI:CD(SD)BR rats were treated with carbaryl, 99.1% purity, by oral gavage at doses of 0 (aqueous 0.5% carboxymethylcellulose/0.1% Tween 80), 0.1, 1.0 or 10 mg/kg/day, day 6 of gestation through day 10 *post partum*. There were 26 per group for the developmental neurotoxicity phase and 6 per group for cholinesterase determinations. Both F0 adults and F1 generation were examined by a Modified Functional Observation Battery. Additional parameters for pups were also recorded including motor activity, brain measurements, development (tooth eruption, eye opening, vaginal opening, preputial separation) and gross and microscopic pathology. Effects on F0 dams at 10 mg/kg/day included autonomic effects and tremors seen during the treatment period, inhibition of RBC, whole blood and brain cholinesterase at 10 mg/kg. Maternal NOEL = 1 mg/kg/day. In the F1 generation, there were no effects on FOB, motor activity, startle response, avoidance, water maze times, body weight, brain morphometric measurements, or pathology. Developmental neurotoxic NOEL = 10 mg/kg/day. No positive control data were included or cited. UNACCEPTABLE but upgradeable with information concerning appropriate positive control studies. No adverse effects. (Gee, 2/16/99)

169 - 391 170648 Supplement to 169-384 166126 Supplement date of June 1, 1999. Authors were K. Robinson and B. Broxup. At the request of US EPA for additional morphometric measurements to assist in the interpretation of the occasional statistically significant differences in specific areas of the brain between the control and high-dose pups and adults, the measurements were repeated. Evaluation of the mid- and low-dose groups was stated as not possible due to the lack of appropriate control tissues with the passage of time. The reevaluation confirmed some of the original findings. These were, again, discounted as treatment-related by the authors based on such criteria as unilateral finding, not seen in both pups and adults, found in one sex only, and not statistically significant based on the adjusted P-value. This submission did not address the positive control data requested by DPR for an upgrade of the study. SUPPLEMENTAL. (Gee, 9/10/99).

#### NEUROTOXICITY, RAT

169 - 396 177090 "An experimental functional observational battery validation study with carbaryl in Wistar rats" (Wahle, M. S., Bayer Corporation, Stilwell, KS, Report 109406, 7/26/00)

The purpose of the study was to validate the procedures of the Functional Observational Battery using untreated animals and animals exposed to a substance with known effects, carbaryl, to serve as positive control data under FIFRA guidelines for neurotoxicity studies. Four technicians were involved. Procedure: Male Wistar Hanover rats (total of 40) were subjected to FOB observations before treatment, 10 animals per technician. Six per group were then given 0 (vehicle: 5% (v/v) ethanol and 5% (v/v) Cremophor EL), 15 or 30 mg/kg carbaryl (99%) by intraperitoneal injection, single dose. At 20 to 90 minutes post-dosing, animals were subjected to an FOB and observed by the four technicians. Compound-related effects at 15 mg/kg included a variety of autonomic signs, alterations in CNS excitability, neuromuscular effects, decreased sensorimotor responses and alterations in activity. The effects at 30 mg/kg were increased in incidence and severity. The observations of each technician were reported and compared. With a few exceptions, there was good agreement among the observers. The study supported the validity and sensitivity of the procedures and training of personnel. Supplemental study. (Gee, 9/20/2000)

#### OTHER INFORMATION

169-390 170647 A Range-finding toxicity study in rats with carbaryl technical® (N. N. Hamada, Hazleton Laboratories America, Inc., Vienna, VA, HLA 656-137, 9/10/90). Carbaryl technical, lot 87191, 99.3% purity, was fed in the diet to CrI:CD7BR rats, 10/sex/group, as follows. Main study animals received 0, 50, 125, 500/4500, 1500/6000 or 3000 ppm for six weeks. The doses were increased after 3 weeks due to a lack of a compound effect. In the supplemental study, 10/sex/group received 0, 300, 6000, 12000 or 24000 ppm in the diet for 4 weeks followed by an extension for an additional 4 weeks (total of 8 weeks) due to a lack of sufficient treatment-related effects. In the main study, hematology and clinical chemistry parameters were measured including plasma, erythrocyte and brain cholinesterase at week 6. In the supplemental study, only cholinesterases were assayed at termination. Body weights were lower at  $\geq 3000$  ppm. Clinical signs were noted at 4500 and above including thin appearance, urine stains, hunched appearance and rough haircoat. At 12000 ppm, 3 females were found dead or sacrificed and at 24000 ppm, 1/sex were found dead. No cause of death was reported by the author but from clinical observations, mortality was probably treatment-related. The NOEL for cholinesterase inhibition was 300 ppm. Systemic NOEL = 1500 ppm (decreased body weight). Supplemental range-finding study. (Gee, 9/30/99)

023, 038359, 038177 and 038178; 1961 review article in Agricultural and Food Chemistry, 9:30-39, by Carpenter et al, summarizing: chronic rat and dog studies, Mellon reports #21-88 and #21-89, in -099, 719 and 718, respectively; mouse subcutaneous oncogenicity, Mellon report not on file; hen neurotoxicity study, Mellon report #21-87, in -134, 37928.

167, 050443; Exact duplicate of 169 - 023 above.

169 - 167, 050446 & -47: Journal article - Weil et al (1972). Current status of tests of carbaryl for reproductive and teratogenic effects. Toxicol. Appl. Pharmacol. 21:390-404. Covers rat reproduction and teratology studies in Mellon Institute reports:

#28-53, teratology and reproduction, in -099, 716;

#29-49, teratology, in -099, 715;

#35-65, reproduction (through F<sub>1a</sub> only), in -099, 712. (No worksheet).

167, 050448 & -49: Journal article - Weil et al (1973). Comparative effect of carbaryl on rat reproduction and guinea pig teratology when fed either [sic] in the diet or by stomach intubation. in Toxicol. Appl. Pharmacol. 26:621-638. Covers rat reproduction/teratology/dominant lethal and guinea pig teratology studies in Mellon Institute reports:

#35-65, rat reproduction (all generations), teratology, and dominant lethal, in -099, 712, 27204, and 27202, respectively;

#34-81, guinea pig teratology, in -099, 713.  
(No Worksheet).

023, 038365: One sentence summary of Mellon Institute chronic dog report #21-89, in -099, 718. Source of summary unknown.

023, 038363: One sentence summary of Mellon Institute rat reproduction report #28-53, in -099, #716. Source of summary unknown,

023, 038364: Two paragraph summary of Mellon Institute rat teratology report #29-49 and guinea pig teratology report #34-81, in -099, 716 or 713, respectively. Source of summary unknown.

023, 038366 and 038367: One paragraph summary of Mellon Institute rat reproduction report #35-65, in -099, 000712. Source of summary unknown.

155, 050427, Exact duplicate of 169-148, 046798, reviewed 10/27/86 by F. Martz. This is a literature review that states carbaryl is a primary neurotoxicant and cites 40 reports on acute toxicity in various species. Data from the open literature indicate that carbaryl can produce developmental toxicity and in some instances, teratogenicity. D. Shimer, 3/24/87.

148, 046798, Exact duplicate of 169-155, 050427, reviewed 3/24/87 by D. Shimer; Literature review of carbaryl entitled "Carbaryl: A Toxicological Review and Risk Analysis," by Morris F. Cranmer, in NeuroToxicology 7:247-332, 1986. This review article concerns material from published articles as well as unpublished information supplied by Union Carbide. Areas covered include neurotoxicity, acute toxicity, developmental toxicity, mutagenicity, immunotoxicity, oncogenicity, human exposure and toxicity, and cancer risk assessment of N-nitrosocarbaryl exposure. Twelve pages of references are provided which include the unpublished Union Carbide reports. F. Martz, 10/27/86.

55, Tab B, no record#; Correspondence dated 5/13/85 from EPA (Douglas D. Camp) to Union Carbide (J.S. Lovell) concerning carbaryl registration standard (no worksheet).

155, 050428; A review article on carbaryl entitled "Carbaryl: A Literature Review," by Michael E. Mont and Frederick W. Oehme, in Residue Reviews 80:1-6-4, 1981. Topics covered include chemistry, toxicity in target and non-target pests, birds, mammals, and humans, metabolism/pharmacokinetics, environmental fate, interactions, analytical methods, and residues. Not reviewed in detail, no worksheet. F. Martz, 5/12/87.

55, 050429; Incomplete copy of EPA's Registration Standard for carbaryl, a partial duplicate of that document located in 169-103, 12895 (no worksheet). F. Martz, 5/12/87.

103, 012895; Contains the Regulatory Position section of the EPA Carbaryl Registration Standard submitted to CDFA by Union Carbide, and is a partial duplicate of material located in 169-155, 50429 (no worksheet). J. Schreider, 5/6/85.