

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

Thiobencarb

Chemical Code # 001933, Tolerance # 00401
SB 950 # 207

7/17/86

Revised 10/20/86, 2/13/87, 6/27/88, and 01/12/96

I. DATA GAP STATUS

Combined toxicity, rat:	No data gap, no adverse effect
Chronic toxicity, dog:	No data gap, no adverse effect
Oncogenicity, mouse:	No data gap, no adverse effect
Reproduction, rat:	No data gap, no 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, no adverse effect
DNA damage:	No data gap, possible adverse effect
Neurotoxicity ¹ :	Not required at this time

¹ An acute and a sub-chronic neurotoxicity study (rat) have been reviewed and are on file. No adverse effect is determined at this time.

Toxicology one-liners are attached.

All record numbers through 131249 were examined.

** indicates an acceptable study.

Bold face indicates a possible adverse effect.

indicates a study on file but not yet reviewed.

File name: T960112

Revised by P. Iyer, 1/12/96

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

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

COMBINED, RAT

086 023498, "Technical Bolero: Combined Oncogenicity and Toxicity Study in Dietary Administration to the Rat", (Life Sciences Research, Ltd., Report # 84/KCI045/579, 10/18/84). Thiobencarb, 95.3% purity, administered in the diet at 0, 20, 100, and 500 ppm for 108 weeks with 60/sex/group (onco portion) and for 104 weeks with 20/sex/group (chronic portion). **No adverse effects reported. NOEL = 20 ppm (weight loss) due to palatability of food. This study (record #s 041795 and 023498) was originally reviewed by Jeff Wong, 6/13/85 and found unacceptable due to lack of individual data, dosing material analysis, appendices and justification of high dose level. Additional information was submitted, reviewed by Jay Schreider, 3/27/86 and the study, subsequently, was identified as **Acceptable**. The NOEL is 20 ppm (approximately 1 mg/kg) based on decreased weight gain. The decreased weight gain can be partially ascribed to palatability problems. There were no apparent effects on cholinesterase; however, negative findings appear due to problems with the assay. **No significant adverse effects were demonstrated by this study.** EPA initially classified this study as supplemental, but has since upgraded the study.

102 through 107 041794 through 041799 are addenda to 023498.

032 971601, 971602, 971604 are summaries of 023498.

060 971610 is an addendum to 023498.

032 971603, interim report of 023498.

081 023497, partial duplicate of 023498.

CHRONIC TOXICITY, RAT

030 971583, invalid IBT study.

021 971586, invalid IBT study.

021 971585, audit of 971583.

015, 027, 028 049985, 033608, summary of 971586.

079 971550, summary information.

CHRONIC TOXICITY, DOG

021 971588, invalid IBT study.

021 971587, audit of 971588.

030 971584, invalid IBT study.

015, 027, 028 033609, 049986, summary of 971584.

090, 91 023500, 037799, "One Year Subchronic Oral Toxicity Study with Thiobencarb Technical in Dogs", (IRDC, # 415-042, 3/20/85). Thiobencarb technical with > 96.2% purity was administered for 1 year by gelatin capsule at 0, 1.8, and 64 mg/kg/day with 6 per group. **No adverse effects reported. NOEL = 1 mg/kg/day (cholinesterase inhibition). **Acceptable.** (Wong, 6/12/85 and Schreider, 3/7/86). The study identified as record # 023500 (also as 037799) was initially reviewed by Jeff Wong and found to be inadequate due to the lack of individual animal data and the analysis of dosing material. Additional information (record # 037800) was submitted, reviewed by Jay Schreider, and considered acceptable. The clinical observations are consistent with cholinesterase inhibition. The changes in hematological values do not appear significant, since there was no statistical significance at sacrifice. The increase in alkaline phosphatase, decrease in alanine aminotransferase, decrease in serum albumin, and slight increase in liver weight at the high dose (64 mg/kg) suggest the presence of a liver effect that is consistent with cholinesterase inhibition and does not appear to be of toxicological significance, especially given the slight magnitude and the lack of histological signs. The NOEL based on cholinesterase inhibition is 1 mg/kg.

084 024209, summary of 023500.

092 037800, appendices (pathology, hematology, etc.) for 023500.

111 047033, EPA review of 023500. Acceptable.

090 048805, addendum to 023500.

ONCOGENICITY, RAT

No study on file.

ONCOGENICITY, MOUSE

046, 047, 048, 049 033521, 033214, 033223, 033213, "Technical Bolero: Potential Oncogenicity in Dietary Administration to Mice, Final Report", (Life Science Research Ltd., Report # 81/KCI0404/527, November 1982). Thiobencarb technical with 93.7% purity was administered in the diet at 0, 25, 100, 400, or 1600 ppm for 2 years with 72/sex/group. **No adverse effects identified. Systemic NOEL = 25 ppm (3 mg/kg) decreased body weight gain, decreased liver weight, and increased kidney weight at 1600 ppm. There were also mild reactive changes in the lungs and liver at 100, 400, and 1600 ppm. While these changes were mild and of questionable toxicological significance, they were treatment related and used to determine NOEL. **Acceptable.** (Wong, 6/16/85).

020 971598, audit of 033521, 033214, 033223, 033213.

032 971600, 034018, summary of 033521, 033214, 033223, 033213.

050 971609, addendum to 033521, 033214, 033223, 033213.

020 971597, protocol for 033521, 033214, 033223, 033213.

REPRODUCTION, RAT

030 971624, invalid IBT study.

035 971633, partial duplicate (amended tables) of 971624.

027 049982, summary of 971624.

034, 035 971631, 971632, adenda to 971624.

094 037804, "A Two-Generation Reproduction Study in Rats with Bolero Technical", (Bio-Dynamics Inc., Project # 82-2615, 12/7/84). Thiobencarb with 96.6% purity was administered by gavage at 0, 2, 10, or 40 mg/kg/day to 30/sex/group through 3 generations. Pup survival NOEL: 10 mg/kg/day. Decreased fertility/pregnancy NOEL: 10 mg/kg/day. Liver effects NOEL: 2 mg/kg/day.

The major problem with the study identified as record # 037804 is the low female pregnancy/male fertility rate in all groups of the F1 generation for production of the F2 generation. For the study to be upgraded to acceptable, the registrant needs to demonstrate that the low fertility/pregnancy rate in the F1 parents did not interfere with the ability of the study to adequately assess the potential of thiobencarb to cause adverse reproductive effects. **Adverse reproductive effects were found at the high dose.** These effects included decreased pup/litter survival, decreased pup weight, and marginally depressed pregnancy/fertility rates. Systemic effects (swelling of the centrilobular hepatocytes) were found in males at the mid and high dose levels. The toxicological significance of the increased testes weight at the high dose is not clear, especially in view of the absence of histological effects. If there were an adverse effect on testes, one would expect the weight to decrease. The increase in weight is probably the result of the decrease in body weight. There was a slight increase in the number of adrenal cortical adenomas in the F1 females (high dose); however, the significance of this finding is unclear, given the levels in historical controls and the small, solitary nature of the adenoma. The NOEL for this study is 2 mg/kg, based on liver effects. It is unlikely that the NOEL would be lowered in the absence of the

low pregnancy/fertility rates of the F1 generation. However, the characterization of the extent and nature of the adverse reproductive effects (currently present at only 40 mg/kg) could be affected. Currently, EPA has classified this study as supplemental. **Unacceptable** and upgradeable. (J. Schreider, 4/7/86).

095, 096, 097, 098, 099, and 100 037805, 037806, 037807, 037808, 037809, and 037810, addenda to 037804.

087 023499, revised version of 1598.

083 024210, partial duplicate of 037804.

042, 056, 061, and 074 971627, 971628, 001597, 001598, 971630, and 042455, addenda to 037804.

042 971626, protocol for pilot study 037804.

061 971629, summary for pilot study for 037804.

122 064700, "Reproduction Study by Oral Forced Administration of Thiobencarb in Rats - Main Experiment", (Central Institute for Experimental Animals, Kawasaki, Japan, Report # ML-289A2, 12/7/87). Thiobencarb with 96.7% purity, Lot # L-6006 was given by oral gavage to Jcl:SD rats, 25/sex/group for two generations at 0, 2, 20, and 100 mg/kg/day, beginning 11 weeks pre-mating for F0 parents and 13 weeks pre-mating for F1s. No effect on reproduction parameters with NOEL \geq 100 mg/kg. Effect on liver and kidneys at mid and high dose levels, decreased weight gain at 100 mg/kg, especially in males. Parental NOEL = 2 mg/kg. **Acceptable** with no adverse effect on reproduction. (Gee, 6/8/88).

030, 034 031141, 031145, invalid IBT reports.

015, 028 033605, summary of 031141.

Summary: The possible adverse effect noted in the study by Bio/Dynamics was not confirmed in the study conducted at the Central Institute for Experimental Animals, Japan. Therefore, there is not an adverse effect on the reproduction at a dose that is not toxic to parental animals. The liver effects were confirmed. The dose at which these were seen is higher than the NOEL's in other studies which will be used to evaluate risk. The route of administration in both reproduction studies was oral gavage as contrasted with the diet in the long-term feeding studies. The palatability of thiobencarb in the diet limited the dose which could be evaluated for other effects including target organs. (Gee, 6/9/88).

TERATOLOGY, RAT

030 971624, invalid IBT study.

034, 035 971631, 971632, audit and validation for 971624.

035 971633, partial duplicate of 971624 with amended tables.

015, 028 033605, summary of 971624.

062 971623, "Teratology Study in Rats with Bolero Technical", (Science Applications Inc., 7/13/82). Thiobencarb with 97% purity was given by gavage at 0, 5, 25, and 150 mg/kg/day on days 6 through 19 of gestation with 27-30 per group. **No adverse effects reported. NOEL: Fetotoxicity = 25 mg/kg/day (skeletal variation and decreased fetal weight), Maternal = 25 mg/kg/day (decreased weight).

The study identified as record # 971623 was initially reviewed by Jeff Wong as unacceptable due to incomplete information. The missing information was supplied (record # 041884) and the study was upgraded to **acceptable**. In the main study, there was a marginal decrease in maternal weight gain. While the change was not statistically significant, there was a clear trend with a marginal decrease at 25 mg/kg/day. The decreased at 150 mg/kg/day is indicative of maternotoxicity. There was evidence of marginal fetotoxicity at 150 mg/kg/day, manifested by decreased fetal weight, increased skeletal variation, and delayed ossification. There was no evidence of terata or embryo/feto lethality. The presence of marginal fetotoxicity at a dose level that also produced marginal maternal toxicity suggests that the fetal effects are attributable to the maternal toxicity and therefore do not represent an adverse effect. (Wong, 6/10/85; Schreider, 3/24/86).

EPA one-liner: maternal NOEL = 25 mg/kg/day, maternal LEL = 150 mg/kg/day; fetotoxic NOEL = 25 mg/kg/day, fetotoxic LEL = 150 mg/kg/day; teratogenic NOEL greater than 150 mg/kg/day; guideline.

032 971616, summary of dose range-finding study for 971623.

036, 037 971618, 971619, 971620, addenda to 971623.

032 971617, summary of 971618.

108, 109 041888, 041889, addenda to 971623.

030, 034 031141, 031145, invalid IBT reports.

015, 028 033605, summary of 031141.

TERATOLOGY, RABBIT

014 971615, invalid IBT study.

015, 027, 028 033606, 049855, 049983, summary of 971615.

052 971621, Bio-Research Labs, 10/29/82 (Wong, 6/9/85). Pilot study for 971611.

058 971622, addendum to 971615.

076 971611, "A Teratology Study in Rabbits with Bolero Technical", (Bio-dynamics Inc., Project No. 83-2705, 12/20/83). Thiobencarb with 96.6% purity was administered by gavage to 18/group at 0, 2, 20, or 100 mg/kg/day during day 7 through 29 of gestation. **No adverse effects identified. Maternal NOEL = 2 mg/kg/day. Fetotoxicity NOEL = 2 mg/kg/day.

The study identified as record # 971611 was reviewed by Jeff Wong. The one-liner was prepared by Jay Schreider. The NOEL for maternal toxicity was 2 mg/kg. The maternal toxicity consisted of decreased weight gain in the mid and high dose groups (statistically significant in the high dose group) and increased premature delivery in the high dose group. The NOEL for fetotoxicity was 2 mg/kg. The fetotoxicity consisted of lower mean fetal weights in the mid and high dose groups which was not statistically significant. The review by Jeff Wong noted a possible adverse effect due to maternal toxicity. **Peer review by Jay Schreider concludes that this is not an adverse effect, but is an indication that the MTD was achieved.** Record # 971621 is a pilot rabbit teratology study conducted with a limited number of animals at 0, 2, 10, 50, or 150 mg/kg. There was NOEL of 50 mg/kg for fetotoxicity (decreased fetal weight) and maternal toxicity (increased incidence of abortions). **Acceptable.** (Wong 6/11/85; Schreider, 7/18/86; J.P., 7/22/86).

EPA one-liner: maternal NOEL = 2 mg/kg, maternal LEL = 20 mg/kg; fetotoxic and teratogenic NOEL not determined due to excessive cannibalization and premature delivery; supplementary.

11 049446, "Teratology Study of Thiobencarb in the Rabbit", (Imamichi Inst. for Animal Reproduction, Japan, 9/86, IIAR No. 158-B). Thiobencarb, lot Z-5005, 96.0% purity; given by oral gavage days 6 - 18 at 0, 20, 100, or 200 mg/kg based on a pilot study (112 049445 with doses of 0, 10, 50, 100, 250, or 560 mg/kg, 5 per group); 16 does per group; maternal NOEL = 100 mg/kg (increased liver weight at 200 mg/kg), developmental tox NOEL \geq 200 mg/kg. **Acceptable with no evidence for a teratogenic or fetal effect. (Gee, 2/13/87).

112 049445, pilot study for 049446.

GENE MUTATION

**020 971637, "The Potential of Benthio carb Technical & Benthio carb Standard to Mutant Histidine-Deficient Strains of Salmonella Typhimurium", (environmental Health & Toxicology., SOCAL 1017/XXV:84, Chevron, 1/6/77). Benthio carb technical SX-796 and Benthio carb standard SX-883 (impurities not stated) tested at 0, 1, 10, 33, 50, 100, or 170 μ g/plate on Salmonella strains TA 98, TA 100, and TA 1537 +/- S9; 100 to 10000 μ g/plate tested at 100; no increase in mutation frequency reported. (Wong, 6/7/85).
EPA one-liner: not a mutagen on Salmonella TA 98, TA 100, or TA 1537 at 50 μ g/plate; minimum.

030, 093 031142, 037801, "Test Report on Mutagenicity of S-(4-chlorobenzyl)-N,N-Diethylthiocarbamate in Micro-Organisms", Thiobencarb technical (95.5%) tested at 0.1% and 5.0% and purified (99.5%) at 1% and 5% and plate incorporation without S9 on Salmonella strains TA 1535, TA 1536, TA 1537, and TA 1538. **No adverse effects noted. Unacceptable** and not upgradeable (no activation, missing strains). (Wong, 6/7/85).

030, 093 031143, 037802, "Test Report on Mutagenicity of S-(4-chlorobenzyl)-N,N-Diethylthiocarbamate in Micro-Organisms", (Institute of Inbiomental Tox., 2/25/74). Thiobencarb technical with 95.5% purity was tested at 0.1% and 5% and purified (99.9%) by disc and plate incorporation without S9 on E. coli strains WP2 her+ and WP her-. **No adverse**

effects reported. Unacceptable and not upgradeable (no activation, missing positive controls). (Wong, 6/7/85).

015, 028 049860, summary of 971637, 031142, 031143.

027 34015, summary of 971637.

093 37801,

CHROMOSOME EFFECTS

030 971645, invalid IBT study.

015, 028 033607, summary of 971645.

020 971648, invalid IBT study.

020 971647, audit report of 971648.

020 971646, "Bolero (Thiobencarb): Dominant Lethal Study in Mice after Acute and Subacute Oral Administration", (Life Science Research, 8/26/78). Thiobencarb with 93.7% purity was tested at 0, 33, 100, and 300 mg/kg/day for 5 days; or at 600 mg/kg in a single dose to 15 males/group by oral gavage; mated 1:2 for 8 weekly periods. **No adverse effects noted.

Acceptable. (Wong 6/7/85).

EPA one-liner: not a mutagen at single oral dose of 600 mg/kg, not a mutagen at oral dose of 300 mg/kg for 5 days; no core grade given.

027 034016, summary of 971646.

113, 118, 119 050062, 060475, 063254, "In Vitro Assessment of the Clastogenic Activity of Benthocarb in Cultured Human Peripheral Lymphocytes", (Life Science Research, England, 9/85, LSR No. 85/KC1050/723). Thiobencarb with 96% purity. Human lymphocytes from a male volunteer; put in culture for 48 hours with PHA, then exposed to a.i. for 24 hours minus activation, for 2 hours with rat liver S9 followed by 22 hours with thiobencarb; 0, 5, 10, 20, or 40 µg/ml based on preliminary cytotoxicity test to 5000 µg/ml; triplicate tubes, single harvest time at 24 hours. **No evidence of increase in aberrations. Acceptable. (JG, 2/13/87).

079 971666, summary information.

027 049984, summary information.

DNA DAMAGE

030 031144, "Test Report on Mutagenicity of S-(chlorobenzyl)-N,N-Diethylcarbamate in Micro-Organisms", (Institute of Inbiomental Tox., 2/25/74). Thiobencarb technical with 95.5% purity and purified with 99.5% purity were tested at 5% and 100% on B subtilis strains H-17 and M-47. Damage repair assay. **No adverse effects reported. Unacceptable** and not upgradeable (two concentrations only, number of plates not stated). (Wong, 6/7/85).

****113, 118, 119 050061, 060476, 063255**, "Micronucleus Test on Mice Treated with Benthiocarb", (Biosafety Research Center, Japan, 1/20/86, AN-PYO Center Report No. 674). Thiobencarb with 96.0% purity was given once at 0, 270, 540, or 1080 mg/kg to 5 males per group and at 0, 405, 810, or 1620 to 5 females per group, or in 4 repeated doses of 0 or 540 mg/kg to males and females by oral gavage; sacrificed at 48 hours after single oral dose (based on a pilot study with harvests at 4, 48, and 72 hours) and at 24 hours after multiple dosings; dose selection based on pilot study. **Increase in micronuclei in polychromatic erythrocytes at high doses. Acceptable.** Note: this test type may fulfill either category 843 (chromosome effects) or 844 (DNA/Other). Because there are two adequate chromosomal studies, this report was considered for the DNA/Other test type. (JG, 2/13/87).

015, 028 049859, summary information.

NEUROTOXICITY

020 971561, invalid IBT study.

020 971560, audit to 971561.

020 971562, "Bolero: Examination for Potential to Cause Delayed Neurotoxicity in Hens", (Life Science Research, Report 78/KC 126/407, 3/11/78). Thiobencarb with 93.7% purity was administered orally at 400, 800, and 1600 mg/kg to 10 hens per group with repeat treatment at 21 days. **Unacceptable** and upgradeable (insufficient information for assessment). The study author concluded that no delayed neuropathic effects were noted. EPA has accepted this study as core minimum with a NOEL of 1600 mg/kg (HTD). Based on experience, EPA has determined that, "of the pesticides causing ChE depression, only the organophosphates have been shown to cause delayed neurotoxicity in the hen. Therefore, it is appropriate to limit this data requirement to those pesticides specified in CFR 40, 158.137."

027 034017, summaries of 97561 and 971562.

145 129882, "An Acute Neurotoxicity Study of Bolero* Technical in Rats", (I.C. Lamb, Ph.D., WIL Research Laboratories, Inc., Ashland, OH., Report # WIL-194010, 8 October 1993). The test article is identified as Bolero* Technical (thiobencarb) with 96.9% purity. 12 or 16 (high dose level) Sprague-Dawley Crl:CD*BR rats per sex per group received a single dose by gavage at concentrations of 0 (0.7% carboxymethylcellulose sodium salt (high viscosity)/1% Tween* 80), 100, 500, and 1000 mg/kg. **Neuropathology is not indicated. Acute Neurotoxicity NOEL = 100 mg/kg (impaired mobility, gait alterations, red material on forelimbs and/or around the nose, yellow and/or orange material on various body surfaces, and reduced motor activity at 500 and 1000 mg/kg). **Acceptable.** (H. Green, and P. Iyer, 1/12/96).

**146 129884, "A Subchronic (13-Week) Neurotoxicity Study of Bolero* Technical in Rats", (Ian C. Lamb, Ph.D., WIL Research Laboratories, Inc., Ashland, OH., Report # WIL-194011, 28 October 1993). The test article is identified as Bolero* Technical (thiobencarb) with 96.9% purity.

10 Sprague-Dawley, Cr1:CD*BR rats/sex/group received 0 (0.7% carboxymethylcellulose (high viscosity)/1% Tween* 80), 2, 20, and 100 mg/kg/day by gavage for 13 weeks. Systemic NOEL < 2 mg/kg/day (Increased red material around nose at 2, 20, and 100 mg/kg/day). Neurotoxicity NOAEL = 20 mg/kg/day (increased axonal degeneration and/or digestion chambers in sciatic, tibial, and peroneal nerves of high dose males compared with controls). **Acceptable.** (H. Green, and P. Iyer, 1/12/95).