

CALIFORNIA DEPARTMENT OF FOOD AND AGRICULTURE
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

METHOXYCHLOR

SB 950-077, Tolerance #120

August 11, 1986

I. DATA GAP STATUS

Chronic rat: Data gap, inadequate studies on file, no adverse effect indicated

Chronic dog: Data gap, inadequate study on file, no adverse effect indicated

Onco rat: Data gap, inadequate study on file, no adverse effect indicated

Onco mouse: Data gap, inadequate study on file, no adverse effect indicated

Repro rat: Data gap, inadequate study on file, possible adverse effect indicated

Terato rat: Data gap, inadequate studies on file, possible adverse effect

indicated

Terato rabbit: Data gap, no study on file

Gene mutation: Data gap, no study on file

Chromosome: Data gap, no study on file

DNA damage: Data gap, no study on file

Neurotox: Not required

Note, Toxicology one-liners are attached

** indicates acceptable study

Bold face indicates possible adverse effect

File name 1b: sb077met.cna

II. TOXICOLOGY ONE-LINERS AND DISCUSSION

CHRONIC AND ONCOGENICITY STUDIES

RAT

No acceptable rat chronic or chronic/oncogenicity studies exist. Chronic findings do not indicate an apparent significant adverse effect. No evidence of oncogenicity was found in the 3 studies examined to date. A general toxicity "NOEL" of 200 ppm should be applied for the present, based on Rec. #038013.

013 913003 A. Oncogenicity, Rat, Hazelton Labs, Vienna, VA, 1978. J. Wong, 4/05/85. B. Methoxychlor, tech. (source not given). C. Time-weighted average doses for males = 845 and 448 ppm, for females = 1385 and 750 ppm. Doses varied over time. D. No chronic toxicity NOEL (dose-related reduction in weight gain of both sexes). No oncogenic effects observed. E. Not acceptable, not complete. Study design deficiencies preclude upgrade. Originally reviewed by J. Wong as Record #913003. Exact duplicate submitted as Rec. #038023 was examined by C. Aldous on 4/24/86. No updated review generated.

021 038023 Exact duplicate of 013 913003, above.

020 038013 A. Chronic, Rat, Kincaid Enterprises, Inc., Nov. 27, 1950. review by C. Aldous, 10/07/85. B. Methoxychlor, grade not specified. C. 0, 25, 200, and 1600 ppm in diet. D. Apparent NOEL = 200 ppm (weight gain decrements in males and females at 1600 ppm). E. Not acceptable nor upgradable: too few animals, limited necropsy data, no blood chemistry data, etc.

020 038019 A. Chronic, rat, Medical College of Virginia, Jan. 20, 1950. Review by C. Aldous 4/22/86. B. Methoxychlor, recrystallized. C. 0, 300, 600, 900, 1200, 2500, and 10000 ppm in diet. D. Apparent NOEL = 1200 ppm (diminished weight gain in both sexes at 2500 ppm. All 10000 ppm females dead by 10 weeks). E. Not acceptable nor complete. Not upgradable. Too few animals per group, too high mortality, etc.

MOUSE

No acceptable studies exist to date. The two studies examined below do not indicate evidence of oncogenic risk. No significant adverse effect is indicated. Toxicity is modest, with an apparent NOEL of 750 ppm, based on diminished body weight gain.

020 038015 A. Combined, mouse, Kincaid Enterprises, Inc., 1/31/73. Review by C. Aldous 4/22/86. B. Methoxychlor, (presumed tech.). C. 0 and 750 ppm levels tested (dietary). D. Apparent NOEL = 750 ppm (HDT). E. Not acceptable, not complete, not upgradable. Only one dosage level employed. Very little individual data.

013 913003 A. Oncogenicity, Mouse, Hazelton Labs, Vienna, VA, 1978. B. Methoxychlor, tech. (source not given). C. Time-weighted average doses of 3491 and 1746 ppm for males, 1994 and 997 ppm for females. Doses varied over time. D. No chronic toxicity NOEL (dose-related reduction in weight gain of females). No oncogenic effects observed. E. Not acceptable, not complete. Study design deficiencies preclude upgrade. Originally reviewed by J. Wong as Record #913003. Exact duplicate submitted as Rec. #038022 was examined by C. Aldous on 4/24/86. No updated review generated.

021 038022 Exact duplicate of 913033, above.

DOG

The one dog study examined is inadequate to meet data requirements. The only useful information obtained is the inference that acute toxicity is minor in the dog.

020 038014 A. Chronic, dog, Kincaid Enterprises, Inc., Nov. 27, 1950. (C. Aldous, 4/22/86). B. Methoxychlor (presumed tech.). C. 0, 20, 100, and 300 mg/kg/day in feed. D. No observed effects: Apparent NOEL = 300 mg/kg/day (HDT). E. Not acceptable, not complete, not upgradable (too few dogs, too little data per dog, etc.).

TERATOGENICITY

RAT

No acceptable teratogenicity study has been received to date. Apparently food aversion is a major factor determining maximum practicable dose in a feeding study. Note that comparatively high dosages were administered by gavage in the Cannon Labs study below (Rec. #038025). The Cannon Labs study is possibly upgradable, and additional information may indicate maternal effects not indicated in the original report. For the present, however, this reviewer must conclude that a **potential adverse effect exists because developmental toxicity is seen at dosages which reportedly do not cause maternal toxicity**. No overall NOEL can be established for the two studies, as gavage and dietary incorporation are not analogous forms of administration.

022 038025 A. Teratogenicity, Rat, Cannon Labs, Inc., Aug. 6, 1976. (C. Aldous, 4/23/86). B. Methoxychlor (Grade and source not given). C. 0, 35, 5.

138, 242, and 346 mg/kg/day (presumed by gavage). D. Maternal toxicity NOEL = 346 mg/kg/day (HDT). Apparent developmental toxicity = 138 mg/kg/day (increased resorptions and dead fetuses at 242 mg/kg/day and above, increased hydronephrosis at 346 mg/kg/day). E. Not acceptable, not complete. Dose levels not justified, test article needs to be identified as to grade, purity, source, etc. File = METHRRT1.077

022 038026 A. Teratogenicity, Rat, Haskell Labs, Sept. 8, 1976. (C. Aldous, 4/24/86). B. Methoxychlor, tech. C. 0, 200, 500, and 1250 ppm in diet (approx. 0, 18, 41, and 97 mg/kg/day). D. Maternal NOEL = 200 ppm (weight gain decrement, decreased food consumption). Developmental effects NOEL = 200 ppm (wavy ribs at 500 and 1250 ppm, pre-implantation loss increases at 1250 ppm). E. Not acceptable, not complete. (No individual data, dosages were apparently less than could have been administered if dosed by gavage, etc.)

REPRODUCTIVE EFFECTS

RAT

Only one reproduction study has been evaluated (Rec. #038024). It is not an acceptable study, nor is the study upgradable, however a potential adverse effect was noted. A marked reduction in fertility, apparently attributable to females, was observed at 1000 ppm level in the diet. Reported parental toxicity was limited to diminished food consumption and diminished weight gain, which effects were seen to a small degree down to the 200 ppm level. **The reduction in fertility was so significant in the second and succeeding generations that a potential adverse effect was noted, despite the fact that**

apparent parental toxicity was observed below levels which caused reproductive effects.

A repeat study is necessary. The registrant may wish to involve gavage dosing rather than dietary exposure if it appears that food aversion may otherwise confound results. Cross-mating may again prove to be a useful adjunct to a follow-up study. See "One-liner" below.

021 038024 A. Reproduction, rat, Haskell Labs, July 15, 1966. (C. Aldous, 4/24/86). B. Methoxychlor, tech. C. 0, 200, and 1000 ppm in diet. D. No NOEL was observed for general toxicological effects (parental generation weight loss, esp. males). The apparent reproductive effects NOEL was 200 ppm (primarily manifest as reduced fertility, especially or entirely affecting females). E. Not acceptable, not complete. Not fully upgradable (only two dosages, no parental histology, etc.).

MUTAGENICITY

GMMU

No study on file

CHROMOSOME

No study on file

DNA DAMAGE/REPAIR

No study on file