

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY  
DEPARTMENT OF PESTICIDE REGULATION  
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

PROPARGITE (OMITE)

Chemical Code # 000445, Tolerance # 00259  
SB 950 # 212

November 24, 1986

Revised 5/1/87, 5/31/88, 11/29/88, 2/9/90, 8/10/90, 7/11/91, 3/19/92, 3/12/93, 7/28/94, 8/7/95,  
6/12/96, 9/28/00

I. DATA GAP STATUS

|                        |  |
|------------------------|--|
| Chronic toxicity, rat: | No data gap, no adverse effect         |
| Chronic toxicity, dog: | No data gap, no adverse effects.       |
| Oncogenicity, rat:     | No data gap, possible adverse effect   |
| Oncogenicity, mouse:   | No data gap, no adverse effects.       |
| Reproduction, rat:     | No data gap, possible adverse effects. |
| Teratology, rat:       | No data gap, no adverse effects.       |
| Teratology, rabbit:    | No data gap, no adverse effects.       |
| Gene mutation:         | No data gap, no adverse effects.       |
| Chromosome effects:    | No data gap, no adverse effects.       |
| DNA damage:            | No data gap, no adverse effects.       |
| Neurotoxicity:         | Not required at this time.             |

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**Toxicology one-liners are attached.**

In the one-liners below:

\*\* indicates an acceptable study.

**Bold face** indicates a possible adverse effect.

All relevant studies through Record No. 176624 (Document No. 259-195) were examined. These include all reports indexed as of 8/9/00.

Note: these pages contain summaries only. Individual worksheets may identify additional effects.

File name: T000928

Updated: [REDACTED], 9/28/00.

## II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

### COMBINED, RAT

**\*\*259-128 089293**, "Combined Chronic Toxicity and Oncogenicity Study in Rats with Omite\* Technical", (Janet A. Trutter, M.S./ D.A.B.T., Hazleton Laboratories America, Inc., Vienna, VA., Report # 798-220, 1/11/91). Omite\* Technical, 87.2% purity [with propylene oxide as stabilizer], fed in the diet for 104 weeks at 0 (Purina\* Certified Rodent Laboratory Chow\* #5002 and corn oil), 50, 80, 400, and 800 ppm to 60 CrI:CD\*BR albino rats/sex/group. General chronic toxicity NOEL = 80 ppm [reduced bodyweights in males at 400 (slight) and 800 ppm, and in females at 800 ppm; corresponding reductions in food consumption in these groups]. **Possible adverse effect:** dose-related incidences of undifferentiated sarcomas of the jejunum were observed, particularly in 400 ppm and 800 ppm males, and in 800 ppm females. Note that current production grade propargite no longer uses propylene oxide as a stabilizer, and an oncogenicity study with the new formulation has been initiated. ACCEPTABLE. (██████████ and ██████████, 7/11/91).

259-128 089294 (Part 11 of 11) Appendix 1 to 128:089293, above. Contains cover letter by R. Cardona et al. (March 8, 1991), which indicates that small intestine tumors seen in study 089293 may have been due to propylene oxide in the technical formulation. This record also contains the re-reading of the intestinal slides of the original study, plus additional step sections of intestines of rats without undifferentiated sarcomas to determine whether test article caused ulceration or crypt abscesses to the intestine (apparently it did). These data were considered in the 7/11/91 review, above.

259-128 089295 (Part 11 of 11) Appendix 2 to 128:089293, above. Study by Banijamali, A.R., and Nag, J.K., "Identification of [Phenyl-U-14C] Omite fecal metabolites in mice and comparison to rat's". Uniroyal Chemical Co., Inc., Middlebury, CT; March, 1991. Primary Project No. 9107. Following single oral doses of Omite (propargite), mice excreted a lower percentage in feces than did rats (42-53% in mice vs. 70-75% in rats). Rat feces contained more unmetabolized propargite than mice, and mouse feces contained higher amounts and apparently a greater variety of polar fecal metabolites than rat feces. This information was submitted to underscore differences in disposition of propargite between these species, only one of which (rat) has been shown to develop undifferentiated sarcomas of the small intestine. No separate Medical Toxicology Branch review is necessary at this time. ██████████, 5/24/91.

259-072 086908 interim data for 128:089293, above.

259-115 090958, Interim Report for 128:089293, above.

**259-156 126295** Goldenthal, E.I., "Two Year Dietary Oncogenicity Study in Rats", IRDC Laboratory Project ID 399-114, 7/12/93. Omite\* (= propargite) Tech., 89.9% a.i. (dietary levels were adjusted for purity) was administered in diets of CD\* male rats for 1 (10/group) or 2 yr (50/group) at 0 and 800 ppm. Test article was the modern tech., containing epoxidized soybean oil as stabilizer. The former tech., containing propylene oxide as stabilizer, had been shown to cause undifferentiated sarcomas in rats (see Record No. 089293), thus this study was done to determine whether the change in stabilizer had eliminated the problem. Body weights and food consumption were statistically significantly reduced in treated rats. The principal toxicological finding was a large number of undifferentiated sarcomas in treated rats, limited almost exclusively to the jejunum. This is a "**possible adverse effect**", and was flagged as such by the registrant, consistent with federal requirements. This study shows that the tumors found in the former study were not the result of the propylene oxide previously used as a stabilizer, since similar tumors were found in the present study, which employed epoxidized soybean oil as stabilizer. The cover letter accompanying this volume (letter dated 9/7/93) noted that mechanistic studies would follow to study the etiology of these tumors. **Acceptable** as a **supplementary study**. ██████████ and ██████████, 7/27/94.

259-141 111356 A timetable for completion of Record No. 126295.

**259-143 113503** An early report of the study in Record No. 126295.

**259-148 119209** A subsequent report of the study in Record No. 126295, with additional data as part of an adverse effects disclosure. [REDACTED], 3/12/93.

**259-033 035292**, "Chronic (2-year feeding studies with D-014 (Omite\*) in rats and dogs". FDRL, 12/29/66. AI (purity not given) administered in the feed at 900, 300, 100, or 0 ppm for 2 years (25/sex/group, except controls, with 37/sex). Additional groups were dosed with 0 (15/sex/group) or 2000 (25/sex/group) ppm for up to 1.5 years. There was reduced survival in 2000 ppm males. UNACCEPTABLE and not upgradeable due to major deficiencies (including group sizes too small, failure to examine tissues of all available animals microscopically, lack of standard descriptions of findings). [REDACTED], 10/18/85. NOTE: Data from this study relating to tumors in the area of the intestines were included on pp. 8-10 of the CDFA review of the 1991 Hazleton study (128:089293). Incidences of masses identified as sarcomas originating in the region of the intestines (excluding reticulum cell sarcomas) were 0, 0, 1, 4, and 4 for controls, 100, 300, 900, and 2000 ppm groups respectively (primarily males were affected). No adverse effects were identified in the 1985 CDFA review, however data support reclassification of this study to indicate a "**possible adverse effect**". Deficiencies in this study make it of lesser value in hazard assessment compared to the 1991 Hazleton study. [REDACTED], 7/11/91)

259-034 and -035 035294-95, Addendum pathology report submitted subsequent to the final report 033 035292. Intestinal tumor data from this re-evaluation were considered along with 033:035292 in the evaluation for the 1991 Hazleton study, 128:089293, above, by [REDACTED] (7/11/91).

259-176 138994 Eldridge, S., "Effect of dietary Omite\* Technical on cell proliferation in jejunum of rats and mice", Pathology Associates, Inc., Durham, NC, Sept. 7, 1994. CD rats and CD-1 mice were given propargite in diet for 1 or 4 wk, in phases as specified below. Osmotic pumps containing BRDU were placed under the skin for the final week of treatment in all cases, to quantitate cell proliferation. The 1-wk phase consisted of male rats at 0 or 800 ppm propargite (89% purity). The 4-wk phase utilized male rats at 0 and 80 ppm, female rats at 0, 40, and 800 ppm, and male mice at 0 and 1000 ppm. Cells which accumulated BRDU in their nuclei were counted by immunohistochemical techniques in the jejunum. Particular areas studied were the muscularis mucosa; and from the tunica muscularis, both the inner circular smooth muscle layer and the outer longitudinal layer smooth muscle layer. Positive proliferation responses were noted as follows: 800 ppm males and females at week 1 (about 3-fold and 4-fold increases, respectively), and 800 ppm males at week 4 [statistically significant ( $p < 0.05$ ), but not considered by investigators to be biologically significant]. Increased proliferation in this study coincided with dose levels which elicited jejunal tumors, and was limited to the rat (the species in which tumors were previously found); thus proliferation may be part of the etiology of tumor development. Useful ancillary information. [REDACTED], 8/2/95.

259-179 138997 Eldridge, S., "Effect of dietary Omite\* Technical on cell proliferation in jejunum of Wistar rats", Pathology Associates, Inc., Durham, NC, 7/18/95. Wistar rats were given propargite in diet for 1 wk. Osmotic pumps containing BRDU were placed under the skin on day 1, to quantitate cell proliferation. Males and females received 0 or 900 ppm propargite (89% purity) during the week of treatment, then sacrificed for examination of jejunal smooth muscle tissues. Numbers of cells which accumulated BRDU in their nuclei were counted by immunohistochemical techniques. Particular areas studied, all from jejunum, were the muscularis mucosa, and (from the tunica muscularis) both the inner circular smooth muscle layer and the outer longitudinal smooth muscle layer. There was no definitive proliferation response. Data of this study and Record No. 138994 together indicate that there are marked strain differences in jejunal smooth muscle cell proliferation response. Investigators concluded that this negative study helped explain why the 1966 FDRL study (Record No. 035292) was negative for treatment effects on undifferentiated sarcoma incidence in the jejunum. It should be noted that DPR does **not** consider that study to be negative. Useful ancillary information. [REDACTED], 8/7/95.

## CHRONIC TOXICITY, DOG

259-033 035293, "Chronic (2-year feeding studies with D-014 (Omite\*) in rats and dogs". FDRL, 12/29/66. Omite\* technical, purity unspecified, in the feed at 900, 300, 100, or 0 ppm; no adverse effects and no evidence of a MTD; insufficient information to assess chronic toxicity; no status change from original review (██████████, 10/18/85) which was UNACCEPTABLE and not upgradeable. ██████████, 11/13/86.

259-036 035296, Pathology addendum to 033 035293, dated 8/84.

259-044 043383, Supplemental information for chronic dog study 033 035293.

\*\*259-127 092005, "A Chronic (1 Year) Oral Toxicity Study in the Dog with Omite\* via the Diet", (Dr. John E. Atkinson, Bio/dynamics, Inc., East Millstone, N.J., Project # 88-3377, 1/10/91). Omite\* Technical, 88.6% purity, was fed in the diet for 1 year (365 to 372 days) to 6 Beagle dogs/sex/group at 0 (Purina\* Certified Canine Diet #5007), 160, 1250, and 1875 ppm (the latter group received 2500 ppm for the first 8 weeks of the study, then on test day 57 and thereafter the concentration was lowered to 1875 ppm). NOEL = 160 ppm in both sexes ["thin" and "dehydrated" appearance, associated with dose-related decrease in body weights, attributable at least in part to reduced food consumption: decreases in RBC parameters (RBC count, HCT, Hb concentration) with associated increases in platelet counts]. The high dose of 1875 ppm was above the tolerated range, resulting in moribund sacrifices of one male and one female. Terminal weights of surviving males and females were 58% and 50% of respective controls, and various serum chemistry alterations appeared to reflect altered nutritional status. High dose tissue effects in both sexes included erythroid/myeloid depletion of sternal marrow and involuted thymus (the latter incidence was increased over controls in 1250 ppm females also). Treatment effects appeared to generally have sharp dose-response relationships, and considering the well-established NOEL at 160 ppm, the study does not present a "possible adverse effect". Study is ACCEPTABLE. (██████████ and ██████████, 7/11/91)

#### ONCOGENICITY, MOUSE

\*\*037-040 035297-035301, "Chronic oncogenic evaluation of Omite\* in CD-1 mice following 78-weeks of dietary treatment". Mouse oncogenicity. FDRL, 2/8/79 (final report of primary study). Primary study reviewed by ██████████, 10/18/85. Additional information (044 043384-043388) considered by ██████████ in 11/4/86 review. Present information, (052 050770-050777) reviewed by ██████████, 4/23/87. Omite\* technical, assayed 88.5% and 84.3% at begin and end of study, respectively. 0, 50, 160, 500, and 1000 ppm in corn oil carrier in diet. No adverse effects. Inadequate evidence of MTD or nearness thereto, however study was judged to be satisfactory for regulatory purposes (see ██████████ review, 11/14/86). Previously considered unacceptable (see ██████████ and ██████████ reviews). Now upgraded to ACCEPTABLE on basis of additional information in Vol. 052 (see below). ██████████, 4/28/87.

259-052 050770-050776, Particularly test article characterization, homogeneity and stability data. Relates to 037-040 035297-035301, above.

259-052 050777, Exact duplicate of 040 035301, except tables unobscured by company confidentiality stamp. Relates to 037-040 035297-035301, above.

259-044 043387, Synopsis of EPA Tox Branch reviews of rat teratology study (027 001015) and mouse oncogenicity study (037 035297) by EPA Registration Division.

#### REPRODUCTION, RAT

\*\*259-111 087974, Kehoe, D.F., "Two-Generation Reproduction Study with OMITE Technical in Rats (Two Litters per Generation)", (HLA, Study No. 6111-108, 1/9/90). Omite Technical, containing 87.2% Propargite (Lot #DJS-032487), was administered in the diet to groups of 25 male and female Crl:CD BR (SD) rats for 2 generations, each with 2 litters, at doses of 0 (corn oil and chow vehicle control), 80, 400, or 800 ppm. Decreased parental food consumption, body weight, and weight gain

were observed at the two highest doses. Decreased pup weight, first observed on day 0 in the high dose and day 7 in the 400 ppm group, persisted through weaning and into the next parental generation. In the initial review, the study was considered ACCEPTABLE, with a Reproductive NOEL = 80 ppm = 4 mg/kg/day (postnatal growth retardation), and a Parental NOEL = 80 ppm = 4 mg/kg/day (decreased weight gain). Growth retardation was considered a **POSSIBLE ADVERSE HEALTH EFFECT** (G. Chernoff, 2/7/90). A review of the supplemental information provided in record no. 088669 did not change the status of this study (██████████, 8/2/90). A cross-fostering study (Vol. 142, see below) demonstrated that pup growth retardation was due to exposure of dams during lactation. (██████████, 3/19/92).

259-142 112732 (ancillary to reproduction study, 259-111:087974), York, R.G., "A cross-fostering reproduction study with Omite\* in rats", IRDC Study ID 399-113, 1/20/92. Charles River Crl: CD VAF/Plus\* rats were assigned to groups of 20 in various cross-fostering combinations. Dams and sires were dosed in diet with 0, 400, or 800 ppm propargite for 70 days prior to delivery. Treatment of dams continued for 3 weeks following cross-fostering of pups on day 1 of lactation. The essential observation was that pup weight gain was inhibited when lactating dams were being treated with 400 to 800 ppm propargite, however prenatal exposure to propargite did not affect pup growth when cross-fostered to control dams. Decreased weight gain of pups whose foster dams received 400 ppm propargite was first observed at day 14. This is consistent with toxicity to pups due to consumption of treated diet, but does not rule out dam-mediated effects. There is no change from the original NOEL, however the extent of concern for reproductive toxicity potential is reduced, since there is no indication of reproductive toxicity during prenatal development. (██████████, 3/19/92).

259-118:095166 protocol for study 259-142 112732, above.

112 088049 Exact duplicate of 111:087974. Noted to library for possible removal.

116 088669, Supplemental information to record 087974, containing a rebuttal by E. Marshall Johnson (██████████, 8/3/90).

033 035292, Reproduction study within combined rat study with same Record number. No useful data; UNACCEPTABLE and not upgradeable due to major deficiencies. (██████████, 10/18/85).

## TERATOLOGY, RAT

**SUMMARY:** Two rat teratology studies with somewhat contradictory results have been submitted and reviewed. In the first study, Record No. 001015, a marginal developmental delay (delayed ossification in hyoid or sternbrae) was observed in the absence of maternal toxicity, and the NOEL was set at 6 mg/kg with a possible adverse health effect noted. In the second study, Record No. 090229, there was no evidence of developmental delay, and no potential adverse health effects were indicated. Since the marginal effects used to set the original NOEL were not replicated, the developmental NOEL was raised to 25 mg/kg, based on the findings of the second study. These findings, a marginal decrease in the number of pups at delivery and an increase in litters with dead pups in the postnatal phase of the study, were not considered to constitute an adverse developmental health effect (██████████, 2/7/90).

\*\*110 090229, "Developmental Toxicity in Rats", (IRDC, Lab. I.D. 399-096, 1/5/90). Omite Technical, containing 85% Propargite (Lot #903N355), was administered by gavage to groups of 45 mated Sprague-Dawley CRL:CD VAF/Plus female rats on days 6-15 of gestation at doses of 0 (corn oil vehicle control), 6, 12, 18, 25, and 105 mg/kg/day. Twenty litters per group were collected by C-section on day 20 of gestation, and the remainder were delivered and raised to weaning. Maternal toxicity (decreased weight gain and increased anogenital staining) was observed during the treatment period in the 105 mg/kg/day treatment group. Developmental effects were limited to the 105 mg/kg/day group, were a decrease in the percentage of live pups delivered, and an increase in the number of litters with dead pups throughout lactation was observed. Maternal NOEL = 25 mg/kg/day (decreased weight gain, anogenital staining); Developmental NOEL = 25 mg/kg/day (decreased pups at delivery, increased litters with dead pups). The study is ACCEPTABLE, and no adverse health effect

is noted (G. Chernoff, 2/5/90).

**\*\*027 001015**, "Teratologic evaluation of Omite Technical in Sprague-Dawley rats", FDRL Lab. No. 5992b, 3/6/79. Omite\* technical, purity unspecified, inferred by CDFA to have been 84-88% purity, based on mouse oncogenicity study of similar time frame. Administration by oral gavage in corn oil vehicle at 105, 25, 6, or 0 mg/kg, days 6-15, necropsy day 20, plug day = 0. No malformations; maternal toxicity NOEL = 25 mg/kg (3 deaths and numerous clinical signs at 105 mg/kg). Developmental toxicity NOEL = 6 mg/kg (increase in minor skeletal variations at 25 mg/kg). Previously considered unacceptable but upgradeable with additional information in reviews by [REDACTED] on 6/14/85, [REDACTED] on 10/10/85, [REDACTED] on 11/10/86, and [REDACTED] on 4/29/87. Submission of dose preparation data in 061 060659 permits upgrade to ACCEPTABLE status, with **possible adverse health effect**. **NOTE:** Developmental effects noted were delayed ossification in hyoid or sternbrae [the latter were classified as "missing" sternbrae, since they could not be visualized following Alizarin-Red treatment to stain ossified tissues], at or slightly above the upper end of the historical range at the testing facility. These developmental delays were flagged as possible adverse effects, even though they were of minor consequence, because they were observed in the absence of apparent maternal toxicity. [Supplementary data enumerated separately, below]. ([REDACTED] 5/26/88, 11/28/88; latter examination noted in rebuttal document only). (CDFA Record 041:035302 is the same study, different format).

EPA 1-liner: Teratogenic NOEL > 105 mg/kg (HDT); Fetotoxic NOEL = 6 mg/kg; Fetotoxic LEL = 25 mg/kg (increased missing sternbrae); maternal NOEL = 25 mg/kg.

052 050778, Supplemental information (especially individual data) for 027 001015.

044 043387-88, Synopsis of EPA Tox Branch reviews of rat teratology study (027 001015) and mouse oncogenicity study (037 035297) by EPA Registration Division.

044 043389, Consultant review of 027 001015 by J. Schardein. Duplicate copy in vol. 060.

027 001014, Historical control data for 027 001015.

061 060659, Dose preparation records for study 027 001015, considered in 5/26/88 review.

015 030286, One-half page summary of rat teratology study; IBT, 11/15/72; Invalid. [REDACTED], 6/13/85.

## TERATOLOGY, RABBIT

**SUMMARY:** The results of two different teratology studies (Record Nos. 259-042:035303 and 259-109:090150) were considered, along with supplementary data and commentaries as noted. Taken together, they indicate a comparatively low NOEL of 4 mg/kg/day for maternal toxicity, although neither study is considered to represent "possible adverse effects" at this time. See CDFA Medical Toxicology Branch rebuttal response of 7/11/91 for analysis of maternal toxicity data from those studies (below) considered together. [REDACTED], 7/11/91.

**\*\*042 035303**, "Teratology study in rabbits: Omite\* technical", Hazleton (Vienna, VA), 3/28/83 (final report). Propargite tech., Lot 0063300, 85% purity; 0, 2, 6, 10, and 18 mg/kg/day in corn oil by gavage. Necropsy day 29, insemination = day 0. Maternal toxicity NOEL = fetal toxicity NOEL = 2 mg/kg/day: Dose-related effects at 6 mg/kg/day or above included: decreased body weight gain of dams during treatment period, increased clinical signs (especially adipisia and anorexia), delayed fetal skull ossification (litter incidence of 3, 3, 6, 4, and 2 in controls through increasing doses). Findings at higher dosages included high mortality in 18 mg/kg/day dams, increased resorptions at 10 and 18 mg/kg/day. Data in Vol. -042 reviewed by [REDACTED], 9/27/85; additional data in 044 043390-92 considered by [REDACTED] in 11/14/86 review: both of these reviewers indicated that additional

information was needed for acceptance. Additional data in 052 050779 were considered by C. Aldous on 4/28/87, and study was judged complete and ACCEPTABLE. Previous data were examined along with newly submitted rat and rabbit acute toxicity data (066 066238 and 066239), and individual maternal toxicity data (061 060660), in 5/13/88 review by [REDACTED]. The latter review did not indicate any change in status of the study. **NOTE:** Data indicate that risk assessment is appropriate, based on the low NOEL for maternal toxicity. No adverse developmental health effect is indicated. [REDACTED] 5/13/88.

EPA classification of study = Core minimum.

044 043390-92, Supplemental information to 042 035303.

052 050779, Supplemental information to 042 035303.

061 060660, Supplemental individual necropsy data for 042 035303.

\*\*259-109 090150 Schardein, J.L., "Developmental Toxicity Study in New Zealand White Rabbits", (IRDC, Lab Project I.D. 399-097, 12/18/89). Omite Technical containing 85% propargite (lot # 903N355) was administered by gavage to groups of 25 inseminated New Zealand White (SPF) rabbits on days 7-19 of gestation at doses of 0 (corn oil vehicle control), 2, 4, 6, 8, and 10 mg/kg/day. No adverse effects were noted. Maternal NOEL (from this study, examined independently from other available data) = 6 mg/kg/day (modest body weight gain decrements at 8 and 10 mg/kg/day; 4 abortions in 10 mg/kg/day does attributed to treatment). Developmental NOEL = 8 mg/kg/day: increased fetal malformations (fused sternebra) were noted at 10 mg/kg/day. In the initial review, the study was considered ACCEPTABLE, with a Maternal NOEL = 2 mg/kg/day (based on apparent treatment effect on abortions at 6 mg/kg/day). The presumed increase in abortions was considered a "possible adverse effect" in CDFA reviews of 1/18/90 and 8/2/90 (both by [REDACTED]). The "possible adverse effect" flag was removed in the 7/11/91 review, on receipt of additional data in 122:091874. [REDACTED], 7/11/91 (see rebuttal, this date, for analysis).

116 088668, Supplemental to record no. 090150, containing a rebuttal by J.L. Schardein ([REDACTED], 8/3/90).

259-122 091874 Supplemental to record no. 090150, containing a rebuttal by J.L. Schardein. Contains recent historical incidence data for abortions, supplies missing individual data on aborting dams, and provides additional interpretative comments. Considered in 1/17/91 rebuttal response by [REDACTED].

## GENE MUTATION

259-184 147642 This document contains the conclusions of the reviewers at U. S. Environmental Protection Agency on seven studies on the genotoxicity of propargite and the metabolite, t-butyl-phenoxy cyclohexyl alcohol. These conclusions were essentially the same as those of the Department. No work sheet. [REDACTED], 6/12/96.

**SUMMARY:** The earlier study (Record No. 066420) was of marginally acceptable quality, having presented some problems in conduct of the study and interpretation of the data. Thus a conservative conclusion of a "possible adverse effect" was reached in connection with accepting the report. Two more recent, well-done studies were undertaken, using DMSO and acetone as acetone as vehicles (Record Nos. 126296 and 126297). These were the same vehicles as were used in Record No. 066420. Comparable treatment times and concentration ranges were used in Record No. 066420 and in the newer studies. The newer studies did not indicate mutagenicity. The overall weight of evidence is that propargite is not mutagenic to CHO cells under test conditions appropriate for the assay. [REDACTED], 7/27/94.

\*\*069 066420, "CHO/HGPRT Mammalian Cell Forward Gene Mutation Assay", (Pharmakon Research International, PA, 9/87, PH 314-UN-001-87). Propargite (Omite technical), no purity stated, sp. g. = 1.085 g/ml; tested with Chinese hamster ovary cells in four trials with DMSO as solvent

and in two trials with acetone as solvent. **Possible adverse effect:** positive increase in mutation frequency at higher concentrations without activation with DMSO, negative results with activation with DMSO and with and without activation with acetone; concentrations ranged from 0.01 to 15 mg/ml; incubation for 5 hours; 7 days expression time, duplicate cultures in each trial; analyses of dilutions for each trial in report; acceptable with a possible adverse genotoxic effect without activation. ACCEPTABLE, [REDACTED], 5/26/88. Rebuttal in 069, dated 9/14/88, states that propargite either reacted with or degraded in DMSO and was negative in acetone as vehicle. The first 2 trials in DMSO, however, were positive with no indication of a problem with stability. No change in status and no worksheet. [REDACTED] 11/29/88.

\*\* 156 126297, "CHO/HGPRT Mutation Assay with Confirmation (Acetone)", (C. Anita H. Bigger, and J.J. Clarke, Microbiological Associates, Inc., Lab Study No. TC864.332001, 8/6/93). Omite Technical, 90% purity, at concentrations of 0 (acetone and untreated) 0.5, 1.0, 1.5, 2, 3, 4, and 5 mg/ml without S-9 mix and at 0 (acetone and untreated), 5, 10, 20, 30, 40 and 50 mg/ml with S-9 mix was tested in two independent CHO/HGPRT mutation assays. Exposure period was five hours. No evidence of mutagenicity with omite treatments under study conditions. The number of mutant colonies were increased with positive controls EMS and B(a)P. ACCEPTABLE. ([REDACTED] and [REDACTED], 7/27/94)

\*\* 156 126296, "CHO/HGPRT Mutation Assay with Confirmation (DMSO)", (C. Anita H. Bigger and J.J. Clarke, Microbiological Associates, Inc., Lab Study No. TC864.332001, 6/16/93). Omite Technical (90%), assayed initially at concentrations of 0 (untreated and DMSO), 1.0, 1.8, 2.6, 3.4, 4.2 and 5.0 ug/ml without S-9 mix and at 0 (untreated and DMSO), 10, 25, 37.5, 50, 60 and 75 mg/ml with S-9 mix and the confirmatory assay at 0.2, 1.0, 1.8, 2.6, 3.4 and 4.2 without S-9 mix and at 10, 25, 37.5, 40, 45 and 47.5 mg/ml (50 mg/ml cytotoxicity only) with S-9 mix in the CHO/HGPRT mutation assay. Exposure period was five hours with a 7-9 day expression time. No concentration-dependent increase in mutants. ACCEPTABLE. ([REDACTED] and [REDACTED], 7/27/94)

043 035304, "Microbial mutagenicity testing on BPPS (Propargite) - Reverse mutation tests with S. typhimurium and E. coli." S. typhimurium strains TA1535, 1537, 1538, 98, and 100 with and without activation; Institute of Environmental Toxicology (Tokyo), 1979; propargite, 91% purity, up to 5000 ug/plate; no mutagenic effect; UNACCEPTABLE and not upgradeable - insufficient replicates, questionable culture characteristics. [REDACTED], 9/27/85.

043 035306, "Mutagenicity evaluation of DO14 final report: Mutagenicity plate plate assay with Salmonella typhimurium and Saccharomyces cerevisiae". S. typhimurium strains TA1533, 1537, 1538, 98, and 100; Litton Bionetics, 5/77; AI not characterized, 0-5 ul/plate; no effects; unacceptable and not upgradeable due to multiple deficiencies. [REDACTED], 9/27/85.

### CHROMOSOME EFFECTS

\*\*043 035307, "Study to evaluate the chromosome damaging potential of D-014 (Propargite) by its effects on cultured Chinese hamster ovary (CHO) cells using an in vitro cytogenetics assay". Microtest Research, Ltd., 6/10/85. 100, 50, 25, or 0 ug/ml without activation; 200, 100, 50, 25, or 0 ug/ml with activation. No increase in aberrations in presence of cytotoxicity. Complete and ACCEPTABLE. [REDACTED], 9/27/85.

\*\* 259-178 138996 Putman, D. L. and R. R. Young "Micronucleus cytogenetic assay in mice" (Microbiological Associates, 10/10/94, G94AP36.122) Propargite, 89.56%, dark amber liquid, was given as a single IP injection at 0 (corn oil), 37.5, 75 or 150 mg/kg body weight to ICR mice. Five per sex were sacrificed at 24, 48 and 72 hours after treatment. There was mortality at 150 mg/kg and clinical signs of lethargy and diarrhea at 75 and 150 mg/kg in both sexes. The proportion of polychromatic erythrocytes to total erythrocytes was decreased in male and female mice at 48 and 72 hours following treatment with 75 and 150 mg/kg body weight. There was no increase in micronucleated erythrocytes. Acceptable. [REDACTED], 8/2/95.



## DNA DAMAGE

\*\*065 065752, "Rat Hepatocyte Primary Culture/DNA Repair Test", (Pharmakon Research International, 7/87, Ph 311-UN-001-87). Omite technical, log # DJS-124, liquid, no purity stated, sp. g. = 1/1 g/ml; tested with hepatocytes from a male Fischer 344 rat isolated at 92% initial viability; tested at 0, 0.0167, 0.05, 0.167, 0.5, 1.67, 5.0, 16.7, 50, 167, 500, 1670 and 5000 mg/ml, 18 - 20 hours, triplicate cultures per concentration; autoradiography with <sup>3</sup>H-thymidine incorporation; scored 50 nuclei per slide for a total of 150 per concentration; cytotoxicity above 0.5 mg/ml so not scored; 2-AAF as positive control. No evidence of unscheduled DNA synthesis as a result of treatment. ACCEPTABLE. [REDACTED], 5/26/88.

043 35305, *B. subtilis* rec assay; Institute of Environmental Toxicology (Tokyo), 1979; propargite, 91% pure, 20 ul of DMSO solution containing up to 100% AI per disc with H17 and M45 strains; no evidence of effects; UNACCEPTABLE and not upgradeable - no replicates or repeats. [REDACTED] 9/27/85.

## NEUROTOXICITY

Not required at this time.

## METABOLISM

259-177 138995 Gay, M.H., "Pharmacokinetics of 14C-Omite: A comparative study in rats and mice". Portions of the study were done in these facilities: Uniroyal Chemical Co., Inc.; Ricera, Inc.; and Batelle. Final report date: 10/21/94. Males and females of both CD rats and CD-1 mice were used in these studies. **Blood pharmacokinetic studies:** Procedures included single oral dose administration (150 mg/kg in corn oil) or single iv administration (not covered in this review). Blood was collected at 0.5, 1, 2, 4, 8, 12, 24, 36, and 48 hr after oral dosing. Peak blood levels were attained sooner in mice than in rats, and clearance was more rapid in mice. Overall bioavailability of dosed propargite was comparable in both species. There were no evident sex differences. **Bile pharmacokinetic studies:** Bile ducts were cannulated for bile collection over a 48-hr period. Duodena were cannulated for infusion of sodium taurocholate to replace collected bile salts. Periodic collection was made of urine and feces, and terminal blood samples were taken. Bile contained 14-18% of the label, without sex or species effects. Urinary label was 10-13% of dose in rats and 3-4% of dose in mice. Feces in these animals (all having bile directly removed by cannula) contained 56-69% of label in rats and 40-50% of label in mice, suggesting moderate absorption in both species. **Metabolite evaluation (bile and plasma):** Pooled samples of bile and blood plasma were radiochromatographed. Propargite and metabolites were identified strictly by elution times compared with standards. No propargite was found in bile, and propargite in plasma was only detectable in male mice. A rapid first step in metabolism was removal of the sulfite group from the cyclohexyl ring, yielding TBPC [i.e. 1-(4-tert-butyl)phenoxy-2-cyclohexanol]. Oxidation of the tert-butyl group was evident in all common metabolites, leading to hydroxymethyl TBPC, a major metabolite. Other common metabolites from plasma or bile possessed one or two additional hydroxyl groups on the cyclohexyl ring. Although there was no exhaustive comparison of metabolites between species or sexes, comparison of chromatograms between sexes or species did not indicate major qualitative differences. Useful ancillary data, although not designed to fill FIFRA guideline requirements. [REDACTED], 8/7/95.

259-195; 176624; "Identification of Metabolites of [1,2,3-<sup>13</sup>C, 2,3-<sup>14</sup>C-Propargyl] Propargite in Male Sprague-Dawley Rats and Male CD-1 Mice: A Comparative Study"; (A.R. Banijamali and N. Fang (Uniroyal), M.C. Savides and M. Watson (Ricera); Ricera, Inc., Painesville, OH and Uniroyal Chemical Company, Inc., Crop Protection Research and Development, Registration Chemistry Section, Middlebury, CT; Uniroyal Study No. 98156, Ricera Study No. 7598-98-0098-AM-001); Five male Sprague-Dawley rats and 40 male CD-1 mice were dosed by oral gavage with 150 mg/kg of [1,2,3-<sup>13</sup>C, 2,3-<sup>14</sup>C-Propargyl] Propargite ([2,3-<sup>14</sup>C-propargyl] Propargite, lot no. CSL-96-696-68-07, radiochemical purity: 99%, specific activity: 28.2 mCi/mmol; [1,2,3-<sup>13</sup>C-Propargyl] Propargite, lot no. AGD-1644-034, purity: 98.9%, % <sup>13</sup>C enrichment: 100%). Urine and feces samples were collected at 24 hour intervals up to 96 hours post-dose. The rats were housed individually in contrast to the mice

which were housed 5 to a cage. In addition, one rat and five mice were treated with the corn oil vehicle, 5 ml/kg. For the male rat, 65.4% of the administered dose was recovered in the first 24 hours with 23.2% in the urine and cage wash and 42.2% in the feces. Likewise, 55.9% of the dose was excreted by the mice in the first 24 hours with 32.5% recovered in the urine and cage wash and 23.4% in the feces. Analysis of the rat and mouse feces samples revealed that 83.3 and 68.2% of the recovered radiolabel was propargite with the remainder being a mixture of many minor metabolites. Two pathways of metabolism were proposed for propargite based upon the metabolites recovered in the urine. The first pathway included the direct conjugation of the compound with glutathione to yield 2-(acetylamino)-3-(2-propynylthio)-2-propenoic acid in both species. The second pathway resulted from the hydrolysis of the 2-propynylsulfite side chain of propargite to form a hypothetical intermediate, propargyl alcohol, followed by glutathione conjugation to form 5 identifiable metabolites in the rat urine and 6 metabolites in the mouse urine. **Study supplemental.** (██████████ 9/7/00)

259-192; 176621; "The Identification of (<sup>14</sup>C)-Omite Urinary Metabolite in Rats"; (A.R. Banijamali and N.J. Tortora; Uniroyal Chemical Company, Inc., Crop Protection Department, Chemistry Section, R & D, Middlebury, CT; Project No. 8706; 9/16/88); A group of 6 male Sprague-Dawley rats were treated with 1.5 mg/kg of (<sup>14</sup>C)-Omite (radiochemical purity: 97.5%, specific activity: 11.6 mCi/mmol, radiolabel on the aromatic ring) which was diluted with non-radiolabeled Omite (lot no. E761-3-10, purity: 95.2%) to an appropriate level of specific activity. Urine and feces were collected up to 72 hours post-dose. Approximately 12% of the administered dose was recovered in the urine. Five radiolabeled compounds were isolated. The 5 metabolites were products of the hydrolysis of the propynyl sulfite side chain, oxidation of the tertiary butyl side chain and hydroxylation of the cyclohexyl ring. **Summary Report.** (██████████, 9/8/00)

259-193; 176622; "The Identification of Omite Metabolites in Rats, Amendment No. 4: Fecal Metabolism of Omite"; (A.R. Banijamali and J.K. Nag; Uniroyal Chemical Company, Inc., Crop Protection Department, Chemistry Section, R & D, Middlebury, CT; Project No. 8706; 11/30/90); In a rat metabolism study, "Metabolism of <sup>14</sup>C-Omite", (project no. 8998), rats were dosed with (1) 25 mg/kg of <sup>14</sup>C-Omite, single dose, (2) 25 mg/kg of <sup>14</sup>C-Omite, preconditioned with 14 doses of 25 mg/kg of unlabeled Omite, and (3) 200 mg/kg, single dose. Fecal samples were collected at 6, 24, 36, 48, 72 and 96 hours post-dose. Peak excretion of the radiolabel was noted between 6 and 24 hours for both sexes in the 3 dosing regimens. Recovery in the feces constituted 51.3 and 61.2% of the administered dose for the males and females in the low dose, respectively. For the high dose group, recovery from the feces of the males and females was 74.5 and 69.9%, respectively, of the administered dose. In the multiple dose group, fecal excretion of the radiolabel constituted 63.3 and 71.7% of the administered dose for the males and females, respectively. Evaluation of the metabolites revealed the presence of 5 radiolabeled compounds in the feces of the males and 4 labeled compounds in the feces of the females. The predominant labeled compound was the parent test material. Its relative abundance in the feces ranged from 40.1% in the low dose females to 84.6% for the high dose males of the total radioactivity recovered. Omite glycol ether constituted from 3.8 to 6% of the total radiolabel recovered in the respective feces samples. The 3 metabolites were products of the hydrolysis of the propynyl sulfite side chain, oxidation of the tertiary butyl side chain and hydroxylation of the cyclohexyl ring. Their sum ranged from 10.4% of the total radiolabel recovered in the feces of the high dose males (total of 3 metabolites) to 56.1% of the total recovered in the feces of the low dose females (total of 2 metabolites). As the dose was increased, an apparently greater percentage of the dose was unabsorbed and passed directly through the intestines. **Summary Report.** (██████████, 9/8/00)

259-194; 176623; "Comparison of Subchronic Vs. Single Oral Dose in the Disposition and Metabolism of Omite in Rats"; (A.R. Banijamali and N.J. Tortora; Uniroyal Chemical Company, Inc., Crop Protection Department, Chemistry Section, R & D, Naugatuck, CT, Biotek, Inc., Woburn, MA and Hazleton Laboratories America, Inc., Madison, WI; Project No. 87122; 6/17/88); Twelve rats/sex/group were fed in the diet 0, 100, 1000 or 2000 ppm of Omite Technical (purity: 87.2%) for 13 weeks. At the conclusion of the treatment period, a satellite study was performed in which 2 rats/sex/dose were treated by gavage with 12.5 μCi of (<sup>14</sup>C)-Omite (radiochemical purity: 97.6%, specific activity: 11.6 mCi/mmol, label on the aromatic ring) (dose of a.i. not reported) and urine, feces and blood samples were collected periodically up to 96 hours post-dose. Radiolabel in specified

tissues was determined and an HPLC profile of metabolites in the urine was obtained from the samples collected over the first 24 hours. For comparison, a pharmacokinetic study was performed in which 2 rats/sex/group were treated by oral gavage with 0, 25, 60 or 200 mg/kg of (<sup>14</sup>C)-Omite (same as above) (specific activity of administered dose not reported). Sampling was performed in the same manner as the subchronic study. Peak urinary excretion for the animals in the satellite study was at 12 or 24 hours post-dose. Peak fecal excretion occurred between 24 and 48 hours for the 100 and 1000 ppm treatment groups. Peak excretion for the 2000 ppm group occurred between 48 and 72 hours. The percentage of administered dose which was recovered ranged from 67.2 to 78.9%. Radiolabel in the tissue samples amounted to 0.9% of the total radioactivity administered. In the pharmacokinetic study, peak urinary excretion was noted at 24 hours post dose. Fecal excretion peaked at 24 to 48 hours for the 20 mg/kg group, 48 hours for the 60 mg/kg group and 72 hours for the 200 mg/kg group. The percentage of the administered dose recovered in the urine was 39.8, 37.3 and 22.5% for the 25, 60 and 200 mg/kg groups, respectively. Radiolabel recovered in the feces constituted 55.7, 74.4 and 72.7% of the administered dose for the 25, 60 and 200 mg/kg groups, respectively. Qualitatively, the profile of the metabolites in the urine were similar in both studies for the different dose levels.

**Summary Report.** (██████, 9/8/00)

## SUBCHRONIC STUDIES

(dermal)

259-191; 176620; "21-Day Repeat Dose Dermal Toxicity Study in Rabbits"; (E.I. Goldenthal; International Research and Development Corporation, Mattawan, MI; Project I.D.: 399-098; 10/26/89); The skin of 5 New Zealand White rabbits/sex/group was treated with 0, 0.1, 1.0, 10 or 100 mg/kg of Omite technical (batch no. 903N355; purity: 86.6%), 6 hours/day, 5 days/week for 3 weeks (estimated as 2.1, 4.5 and 12.5 and 28 ng/cm<sup>2</sup>, 15 total number of doses). No apparent treatment-related effects were noted for mean body weight and food consumption. Increasingly severe dermal irritation was noted over the course of the treatment period with even the 0.1 mg/kg animals exhibiting severe erythema and moderate edema at the termination of the study. The 100 mg/kg animals suffered severe erythema and severe edema by the third dose with fissuring, blanching, eschar, coriaceousness and exfoliation evident by the end of the second week. No signs of systemic toxicity were noted. No treatment-related effects were evident for the hematology and clinical chemistry. In the microscopic examination of the liver and kidneys of the high dose group, there was an increased incidence of hepatic inflammation and necrosis and chronic nephritis. Examination of the treated skin indicated a dose-related incidence of acanthosis, hyperkeratosis and inflammation for animals treated with 0.1 mg/kg and above. **No adverse effect indicated. (NOEL): Systemic (M/F):** 10 mg/kg/day (based upon the increased incidence of lesions in the kidneys and liver of the 100 mg/kg treatment group); **Irritation (M/F) < 0.1 mg/kg/day** (based upon the irritation effects noted for the 0.1 mg/kg treatment group). **Study acceptable.** (██████, 9/6/00)