RC

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

005537

SEP - 3 1985

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Telone II (1,3-dichloropropene) Registration Standard

TO: Henry Jacoby
Product Manager Team 21
Herbicide/Fungicide Branch
Registration Division (TS-767C)

THRU: Laurence D. Chitlik, D.A.B.T.
Section Head, Section V
Toxicology Branch
Hazard Evaluation Division (TS-769C)

LDC 8/30/85

THRU: Theodore M. Farber, Ph.D.
Chief, Toxicology Branch
Hazard Evaluation Division (TS-769C)

W.J.Burns 9-3-85

Attached is the Toxicology Chapter for Telone II (1,3-dichloropropene) Registration Standard. Included are the following:

1. Summary of toxicology data for Telone II
2. Update TOX "One-liners"
3. Data summary table which indicates TOX data gaps
4. Bibliography
5. Evaluation of all studies reviewed during the course of this standard

Due to the potential carcinogenicity of Telone II, the Toxicology Branch peer review panel will meet on September 9, 1985 to discuss and evaluate the toxicology data submitted. Risk assessment for Telone II will be performed after the peer review committee meeting and will be forwarded to you when available.

Quang Bui

Quang Q. Bui, Ph.D.
Toxicologist
Review Section V, Toxicology Branch
Hazard Evaluation Division

cc. Dr. Amy Rispin (SIS)
Robert Coberly (TOX)

176

TOXICOLOGY DATA SUMMARY

ACUTE TOXICITY

Acute oral toxicity in the rat (Torkelson and Oyen, 1977) places Telone II (a mixture of cis and trans-1,3-dichloropropene, 92%) in Toxicity Catogory II. The acute oral LD50s for female and male rats were determined to be 470 and 713 mg/kg, respectively. The acute oral LD50 in the mouse was 640 mg/kg for both males and females (Toyoshima et al., 1978; Toxicity Category III). The dermal LD50 was determined to be 504 mg/kg for both sexes of rabbits (Dow Chemical Co, 1978) with moderate to severe erythema and edema observed (Toxicity Category II). A primary dermal irritation study conducted in rabbits (Dow Chemical Co., 1978) found slight to moderate erythema at both intact and abraded skin sites after 24 hours (Toxicity Category III). Severe conjunctival irritation and moderate corneal injury were observed in rabbit eyes instilled with 1/10 ml of Telone II (Dow Chemical Co., 1978). However, complete recovery occurred in all animals by the eighth day (Toxicity Category II). An acute inhalation toxicity study conducted with a mixture of cis- and trans-1,3-dichloropropene (94.5%) indicated a LC50 of 729 ppm/4 hours in rats (Tunstall Lab., 1977).

Rosenblum and Talley (1979) investigated the performance of conditioned tests by Rhesus monkeys after acute inhalation exposure to Telone II. A deficit in performance was observed in animals exposed to 400 or 600 ppm dose levels. However, the small number of animals used (4) and the questionable reliabity of the parameters measused precluded a meaningful assessment of the data (Supplementary Data).

Human volunteers exposed to 1,3-dichloropropene via inhalation at 1 or 3 ppm for 1 to 3 minutes reported "fatiguing of the sense of smell" (Torkelson et al., 1973). However, this study was of only very limited utility due to limitations of the study design and conduct (Supplementary Data).

1,3-dichloropropene should thus be considered as Toxicity Category II for oral toxicity and primary eye irritation, and Toxicity Category III for dermal irritation. The acute inhalation and acute dermal studies are classified as Core Supplementary Data and need to be repeated. No dermal sensitization studies were conducted.

SUBCHRONIC TOXICITY

Toxicology Branch files contained several subchronic studies with 1,3-dichloropropene in laboratory animals.

Groups of 10 Fischer-344 rats and 10 CD-1 mice of each sex were exposed to Telone II vapors at 0, 3, 10, or 30 ppm, 6 hours/day, 5 days/week for 4 weeks (Coate et al., 1978). Clinical observations were made daily and body weights were recorded at study initiation and weekly thereafter. At study termination, all animals were subjected to a complete necropsy. Histopathologic examinations were conducted on selected tissues (lung, heart, kidneys, brain, liver, and gonads).

Changes from controls in body weight gains, necropsy findings, or histopathological examinations were not apparent in treated mice and rats at any of the dosage levels tested. The NOEL for both rats and mice was determined to be 30 ppm (highest dose tested) and this subchronic inhalation study (Coate et al., 1978) is classified as Core Minimum Data.

A subchronic inhalation study exposing rats, guinea pigs, rabbits, and dogs to 1,3-dichloropropene (cis isomer 46%, trans isomer 53%, and epichlorohydrin 1%) was conducted over a period of 6 months by Torkelson et al. (1973). Groups of 12 rats per sex, 12 guinea pigs per sex, 3 rabbits per sex, and 2 dogs per sex were exposed to 1 or 3 ppm of the mixture for 7 hours/day, 5 days/week for 6 months.

The investigators reported that cloudy swelling of the renal tubular epithelium was the only histopathologic change observed in male rats of the 3 ppm exposure level. No compound-related effects were noted in guinea pigs, rabbits, and dogs relative to body weight, clinical signs, necropsy and histopathologic changes. However, this study is classified as Core Supplementary Data since only a summary of findings was reported and the small numbers of dogs (2/sex/dose level) and rabbits (3/sex/dose level) used precluded meaningful assessment of the data.

A 90-day inhalation study with Telone II (47% cis-, 45% trans-1,3-dichloropropene) was investigated by Coate et al. (1979a) in both Fischer-344 rats and CD-1 mice. Groups of 10 rats or mice per dose per sex were exposed to 0, 10, 30, or 90 ppm of Telone II for 6 hours/day, 5 days per week. Actual concentrations of 11.9, 32.1 and 93 ppm were obtained and were equivalent to 0.055, 0.146, and 0.423 mg/L, respectively. All animals were observed daily and body weights were recorded weekly. Gross and histopathologic examinations were performed at study termination.

Compound-related increases in mortality were not apparent in either rats or mice. Significantly lower mean body weights were reported in female rats and mice exposed at 90 ppm throughout the entire investigation. Effects on mean body weight of rats and mice at the 10 and 30 ppm were not apparent. No compound-related gross pathology was reported for mice. However, a dose-related increase in the incidence of kidney discoloration with reddened medullas was found in treated rats. Treatment related histologic lesions in the

epithelium of nasal turbinates were observed in 30 ppm female rats, 90 ppm male and female rats, and 90 ppm female mice. Because of the lack of urinalysis and hematology measurements, this study is classified as Core Supplementary Data with a systemic NOEL tentatively determined to be 10 ppm (0.055 mg/L; lowest dose tested).

A 90-day feeding toxicity study with Telone (a mixture of cis-1,3-dichloropropene 40.2%, trans-1,3-dichloropropene 38.3%) was conducted in Wistar rats by Til et al. (1973). Groups of 10 males and 10 females each were gavaged with 0, 1, 3, 10, or 30 mg/kg/day of the mixture, 6 days/week for 13 weeks. Body weights were recorded weekly. However, the food consumption was measured weekly only during the first four weeks and on weeks 11 and 12. Clinical chemistry, gross and microscopic examinations, urinalysis, and organ weights were measured at study termination.

Biologically significant differences in body weight gain and food consumption were not found. No compound-related effects with respect to hematology, clinical chemistry, necropsy, and histopathologic examinations were observed. The only observable toxic effects were the increase in kidney weights noted in males of the 10 mg/kg groups and in both male and female rats of the 30 mg/kg group (highest dose tested). Since only a tabulated summary of all findings was submitted, none of the reported data could be substantiated in the absence of individual supporting data. At the present time, a NOEL could not be established and this study (Til et al., 1973) is classified as Core Supplementary Data pending the submission of additional requested data.

CHRONIC TOXICITY

Chronic toxicity was evaluated in the carcinogenic assay with Telone II (a mixture of cis-1,3-dichloropropene 45%, trans-1,3-dichloropropene 47%, 1,2-dichloropropane 2%, and epichlorohydrin 1%) in rats conducted by the National Toxicology Program (NTP, Publication 84-2525, 6/84). Groups of 50 male and female rats were gavaged with 0, 25, or 50 mg/kg/day in corn oil, 3 days a week for 104 weeks. Body weight, clinical chemistry, and hematology determinations were conducted at several intervals during the investigation. Only non-neoplastic effects are discussed below; see the section on oncogenicity for a discussion of neoplastic findings.

Administration of Telone II up to and including a dosage level of 50 mg/kg was not associated with body weight reduction. No compound-related significant changes in mortality rate or hematology were observed in both sexes of all treated groups. However, dose-related decreases in serum cholinesterase levels with statistical differences noted at the 50 mg/kg dosage level were found in the treated females but not in males. The levels of lactic acid dehydrogenase were also significantly reduced in both sexes of the 50 mg/kg dosage level. The NTP study (1984) also reported an increased incidence of forestomach basal cell hyperplasia in males and females of all treated groups. The percentages of males and females displaying this histopathologic lesion were 3, 14, and 35%, and 0, 6, and 40% for the 0, 25, and 50 mg/kg groups, respectively. An increase in kidney nephropathy was also observed in treated females being 29%, 48%, and 48% for the groups receiving 0, 25, and 50 mg/kg, respectively. Edema of the urinary bladder was also found but only in males (17%) and females (6%) of the highest dose tested (50 mg/kg). Under the conditions of this investigation, the systemic NOEL is determined to be < 25 mg/kg/day (lowest dose tested). The chronic section of this NTP study (1984) is classified as Core Supplementary Data due to limitations of the study design (only two dose levels used, lack of food consumption, urinalysis and ophthalmologic examinations, and hematology and clinical chemistry conducted only up to week 69).

The NTP mouse carcinogenicity assay (NTP, Publication 84-2525, 1984) was not designed to fully assess chronic toxicity. Parameters commonly used to evaluate long term toxicity were not measured. Clinical chemistry, hematology, food consumption, urinalysis, and ophthalmology were not determined. However, several chronic effects were noted by the study authors in addition to positive oncogenic findings. Treatment-related non-neoplastic effects in mice consisted of significantly reduced female survival rate at 100 mg/kg and dose-related increases in the incidences of urinary bladder epithelial cell hyperplasia in both males and females at 50 and 100 mg/kg dosage levels.

At this time, the registrant has not fulfilled the requirement for chronic toxicity testing of Telone II in two species. It should be noted that the registrant has indicated that a chronic inhalation study with 92% 1,3-dichloropropene and 2% epoxidized

soybean oil as stabilizer will be conducted in rats and rabbits. Final reports are expected in 1988.

ONCOGENICITY

The oncogenic potential of Telone II (a mixture of cis-1,3-dichloropropene 45%, trans-1,3-dichloropropene 47%, epichlorohydrin 1%, chlorinated propenes and hexenes 5%) was investigated in rats and mice.

Groups of 52 Fischer-344 rats/sex each were exposed to 0, 25, or 50 mg/kg/day of Telone II (by gavage in corn oil), 3 days/week for 104 weeks (NTP-Publication 84-2525, 6/84). Body weight, clinical chemistry, and hematology were measured at several intervals during the investigation. Complete necropsy and histopathologic examinations were conducted on all animals that died during the study, or were sacrificed at interim periods or at study termination.

Forestomach squamous cell papillomas were found in both sexes. This neoplasm rarely occurs in female rats (0% incidence in the concurrent vehicle control group) but was found at 3% and 10% in females of the 25 and 50 mg/kg dosage levels. Positive trend increases in the incidences of forestomach squamous cell papillomas and carcinomas were also found in treated male rats. These incidences attained statistical significance for males of the 50 mg/kg group. In the liver,a positive trend increase in neoplastic nodules was found in treated males with statistically significantly higher incidences observed at both dosage levels as compared to controls. The frequency of liver tumors in treated females was not biologically different from that of controls. However, positive trend increases in the incidences of mammary gland adenomas/fibroadenomas and thyroid follicular cell adenomas/carcinomas were observed in the treated females. From the above findirgs, there is sufficient evidence of oncogenicity as characterized by increased incidences of squamous cell papillomas and carcinomas of the forestomach and neoplastic nodules of the liver in males and increased incidences of squamous cell papillomas of the forestomach in females. The oncogenicity study in rats with Telone II (1% epichlorohydrin) is classified as Core Minimum Data.

Groups of 50 B6C3F1 mice per sex were gavaged each with 0, 50, and 100 mg/kg/day of Telone II in corn oil, 3 days/week for 104 weeks (NTP Publication 84-2525, 6/84). Body weight was recorded and gross and histopathologic examinations were conducted. Clinical chemistry and hematology were not measured. Three shipments of mice were received at Frederick Cancer Research Center and randomization of the animals was not performed at study initiation. Animals of the vehicle control group were from the first shipment whereas those of the 50 mg/kg group were from the first and second shipments and those of the 100 mg/kg group were from the second and third shipments. Consequently, disparity relative to the initial body weight and age of the animals among all groups was evident in this study and restricts its usefulness.

Twenty-five control male mice (50%) died during weeks 48-51. The investigators stated that suppurative inflammation of the heart (myocarditis) was the causative factor. Due to excessive mortality encountered in the control males, only 8 animals were sacrificed at study termination. The limited number of control males at study termination would therefore restrict the statistical reliability as well as the biological significance of all findings in this study. Since over 50% of control male mice died during the first year, a time when neoplastic lesions are not expected to occur, all neoplastic findings in the treated males must therefore be compared with those of the historical control data provided. In females, statistically significant increases in the incidence of urinary bladder transitional cell carcinomas were found at the 50 and 100 mg/kg dosage levels. Respective incidences of 0%, 16%, and 44% were found in females. In males, carcinomas of the urinary bladder were only found in 2 animals of the 100 mg/kg dose level. The incidences of hepatocellular adenomas, carcinomas, or adenomas combined with carcinomas of the treated males were within the historical control range (31.4%). Significant increases in hepatocellular adenomas and carcinomas was found in females of the 50 mg/kg group but not at the 100 mg/kg dosage level. Squamous cell carcinoma of the forestomach was not found in control and treated males but was observed in 2 females of the highest dose group. Forestomach squamous cell papillomas were not found in either male or female controls but were detected in 4 and 6% of the males and in 2 and 4% of the females in the 50 and 100 mg/kg groups, respectively. Squamous cell papillomas of the forestomach is considered as a rare tumor in mice (historical control data of 0.6% and 0.3% for male and female, respectively). Therefore, this neoplasm apparently was compound-related. In the male, compound-related and significant increases in the incidences of lung adenomas and lung adenomas combined with carcinomas were found. The incidences of lung adenomas found in terminally sacrificed males were 0%, 9%, 25%, 23% for the concurrent control, historical control, 50, and 100 mg/kg groups, respectively. Statistically significant increases in the incidences of lung adenomas and lung adenomas combined with carcinomas were also noted in females. The incidences of female mice with lung adenomas at terminal sacrifice were 0%, 3.3%, 7%, and 19% for the concurrent control, historical control, 50, and 100 mg/kg groups, respectively.

Treatment-related non-neoplastic effects in mice consisted of a significantly reduced female survival rate at 100 mg/kg and dose-related increases in the incidences of urinary bladder epithelial hyperplasia in both males and females at the 50 and 100 mg/kg dosage levels.

Although several deficiencies in the mouse study design and conduct were noted, there is still sufficient evidence of oncogenicity in female mice as characterized by increased incidences of forestomach squamous cell papillomas, urinary bladder transitional cell carcinomas and alveolar/bronchiolar adenomas and carcinomas. There is limited evidence of oncogenicity in male mice (due to excessive mortality in control males) as characterized by increased incidences of forestomach squamous cell papillomas, urinary bladder transitional cell

carcinomas, and alveolar/bronchiolar carcinomas and adenomas. The mouse study (NTP, 6/84) is classified as Core Supplementary Data due to the study limitations.

From the above findings, forestomach squamous cell papillomas were observed in both rats and mice gavaged with Telone II containing 1% epichlorohydrin as a stabilizer (NTP, Publication 84-2525, 6/1984). The presence of epichlorohydrin in Telone II should be of concern since epichlorohydrin is a known carcinogen and mutagen. Konishi et al. (1980) reported that epichlorohydrin caused forestomach papillomas in Wistar rats at 750 and 1500 ppm in drinking water. Forestomach papillomas or carcinomas were also observed in male and female rats gavaged with 2 mg/kg/day epichlorohydrin for 104 weeks (Wester et al., 1984). The presence of a similar type of neoplasm (forestomach squamous cell papilloma) in all these studies involving epichlorohydrin suggest that epichlorohydrin may have a contributive role in the oncogenic potential of Telone II in both rats and mice. However, since neoplasms other than forestomach papillomas or carcinomas were also found in these NTP studies with Telone II (e.g. urinary bladder transitional cell carcinoma, liver neoplastic nodules, lung adenomas and carcinomas, thyroid follicular cell adenomas or carcinomas, etc,...), it can be concluded that both 1,3-dichloropropene and epichlorohydrin are positive oncogens.

Van Duuren et al. (1979) reported that weekly subcutaneous injections of cis-1,3-dichloropropene in female mice at 3 mg/mouse/week for 77 weeks resulted in significant increased incidences of fibrosarcomas at the site of injection. The number of female mice with fibrosarcomas was 6/30 as compared to 0/100 control animals. However, dermal application of cis-1,3-dichloropropene at 122 mg/mouse, 3 times a week, did not significantly increase the incidences of skin papillomas (Van Duuren et al., 1979). Cis-1,3-dichloropropene was also inactive as a mouse skin oncogen when tested as an initiator with PMA as the promoter (Van Duuren et al., 1979). The Van Duuren et al. (1979) study is classified as Core Supplementary Data due to limitations of the reported data.

In conclusion, there is sufficient evidence to suggest that Telone II (1% epichlorohydrin) is an oncogen in both rats and mice. The stabilizer epichlorohydrin used in Telone II may have influenced the development of forestomach squamous cell carcinomas or papillomas in both rats and mice. However, it should be noted that the registrant in a Confidential Statement Formula submitted to the Agency on 2/28/85 indicated that the stabilizer epichlorohydrin had been replaced with epoxidized soybean oil. Therefore, to fully understand the oncogenic potential of the newly formulated Telone (without epichlorohydrin), it is required that chronic/oncogenic studies be performed with the new formula.

TERATOGENICITY

The teratogenic potential of inhaled Telone II (a mixture of cis-1,3-dichloropropene 47.7%, trans-1,3-dichloropropene 42.4%, and epichlorohydrin 1%) was investigated in Fischer 344 rats and New Zealand rabbits (John et al., 1983). Bred rats and inseminated rabbits were exposed to 0, 20, 60, or 120 ppm (equivalent to 0, 0.091, 0.272, or 0.545 mg/L air) of Telone II, 6 hours/day, during gestation days 6-15 or 6-18, respectively.

In rats, maternal toxicity was demonstrated at all dosage levels tested (maternal NOEL < 20 ppm, lowest dose tested) as evidenced by significant decreases in body weight gain and food consumption during the exposure period. No evidence of teratogenicity was noted at the dose levels used in this study. Embryo/fetotoxicity was apparent at the 120 ppm dosage level as characterized by a significant increase in the litter and fetal incidences of delayed ossification of the vertebral centra. However, since only a tabulated summary of all findings was submitted, all the reported findings could neither be confirmed nor verified. The rat inhalation teratology study is classified as Core Supplementary Data due to limitations in the available study data. Conclusions relative to developmental toxicity (embryo/fetotoxicity) will await the submission of requested additional data.

Evidence of teratogenicity was not apparent in the rabbit inhalation teratology study (John et al., 1983). Signs of maternal toxicity were found at the 60 and 120 ppm dosage levels as characterized by decreased maternal weight gain during the exposure period (days 6-18 of gestation). Evidence of embryo/fetotoxicity was not apparent in any of the treated groups including the highest dose used (120 ppm). However, all maternal and fetal findings were summarized and reported as means. Supporting individual data, necropsy data, and fetal data were not submitted and precluded meaningful assessment of the reported data. The rabbit inhalation teratology study is classified as Core Supplementary Data with a maternal NOEL tentatively determined to be 20 ppm (lowest dose tested). Conclusions relative to developmental toxicity (embryo/fetotoxicity) will await the submission of requested additional data.

It should be noted that if residues of 1,3-dichloropropene are found in feed/food commodities, teratology studies using the feeding route of administration must also be considered.

REPRODUCTIVE EFFECTS

The effects of inhalation exposure to Technical D-D "epichlorohydrin free" (a mixture of cis-1,3-dichloropropene 28.1%, trans-1,3-dichloropropene 25.6%, 1,2-dichloropropane 25.6%, 2,3-dichloropropene 5.0%, 3,3-dichloropropene 4.8%, other chlorinated hydrocarbons 4.47%, epichlorohydrin < 1%) on mating behavior and fertility of rats was investigated by Clark et al. (1980). Male and female Wistar rats were exposed to Technical D-D for 6 hours/day, 5 days/weeks at concentrations of 0, 64, 145 or 443 mg/m^3 expressed as the sum total of the two isomers of 1,3-dichloropropene plus 1,2-dichloropropane. After 2, 4, 7, and 10 weeks of exposure, 20 males from each group were evaluated for reproductive performance. Each male was housed with two unexposed females every night for 7 days. The reproductive capabilities of 15 females per exposure level were assessed after 10 weeks of exposure. Each female was housed for 7 days with one unexposed male of proven fertility. Gross and histopathologic examination with emphasis on organs of the reproductive tract were performed.

No effects of treatment on the mating, fertility or reproductive indices of males or females were apparent. Estrous cycling was similar in control and treated females. There were no apparent effects on pre- and post-implantation loss, gestation index, gestation length, litter size, sex ratio, pup appearance, pup weight, as well as pup survival index. Microscopic observations did not indicate any compound-related histopathologic changes which could be attributed to Technical D-D exposure up to and including the highest dose used (443 mg/m^3).

Although no adverse reproductive effects were observed, the results obtained from this study could not be applied to Telone II since Technical D-D contains only 53.7% of cis and trans-1,3-dichloropropene whereas Telone II includes 92% of cis and trans-1,3-dichloropropene. The Clark et al.' study (1980) is classified as Core Supplementary Data.

A reproductive study with Telone II is presently lacking. However, the registrant (Dow Chemical) indicated that an inhalation two generation reproduction study in rats will be initiated in 1985 using a product containing 94% 1,3-dichloropropene and 2% epoxidized soybean oil as the stabilizer. According to the registrant the report will be issued in 1987.

MUTAGENICITY

The FIFRA Guidelines, Subdivision F state that the mutagenic potential of a given chemical must be assayed for 3 categories of genetic defects: (1) gene mutation, (2) structural chromosomal aberrations, and (3) other mutagenic mechanisms, including DNA damage/repair.

From gene mutation tests, there is sufficient evidence to indicate that 1,3-dichloropropene (Telone II, a mixture of cis and trans 1,3-dichloropropene) as well as the individual cis and trans isomers of 1,3-dichloropropene are direct acting microbial mutagens that function primarily by base-pair substitution.

Brooks et al. (1978) indicated that positive mutagenic responses were observed with "purified inhibited 1,3-D" (DD 95, a mixture of cis-1,3-dichloropropene 51.3%, trans-1,3-dichloropropene 43.7%, and epichlorohydrin 0.6%) in strains TA-1535 and TA-100 in both the presence and absence of metabolic activation (S-9 mix). However, negative results were obtained from assays conducted with strains TA-1538 and TA-98. These findings suggest that this mixture is a mutagen in microorganisms by the induction of base-pair substitution. Flessel (1977) and Sudo et al. (1978) also reported positive results with 1,3-dichloropropene in strains TA-1535 and TA-100. Further, Sudo et al. (1978) found positive results in strain TA-98 in both the presence and absence of metabolic activation and in strains TA-1537 and TA-1538 but only in the presence of S-9 mix.

DeLorenzo et al. (1977) investigated the mutagenic potential of a Telone commercial product (mixture of cis-1,3-dichloropropene 30%, trans-1,3-dichloropropene 30%, 1,2-dichloropropane 20%, 2,3-dichloro-1-propene 5%, and allyl chloride 2%). They reported that positive results were obtained in strains used to detect base-pair substitution (TA-1935 and TA-100) and frame shift mutation (TA-1978) in both the presence and absence of metabolic activation. The lowest concentration of the Telone commercial product that induced a positive effect in these strains was 100 ug/plate (lowest dose tested).

DeLorenzo et al. (1977) also reported that both the cis and trans-1,3-dichloropropene gave positive results in TA-1535, TA-100, as well as in strain TA-1978. Brooks et al. (1978) found positive results in TA-1535, TA-100, and TA-98 when 99% pure cis-1,3-dichloropropene was used, although a negative response was obtained in non-activated cultures of TA-1538.

Negative results were obtained with Telone II from a reverse mutation assay with E. Coli B/r Wp2 (Sudo et al., 1978). However, Telone II was negative in the mouse host mediated assay with Salmonella typhimurium G 46 as indicator for reverse mutation (Shirasu et al., 1976; Sudo et al., 1978).

No further testing is required relative to gene mutation assays with 1,3-dichloropropene.

The mutagenic potential of 1,3-dichloropropene relative to structural chromosomal abberations is not known with certainty. Venable et al. (1980) indicated that workers engaged in the manufacture of glycerine are also exposed to 1,3-dichloropropene, allyl chloride, and epichlorohydrin. No significant difference in the incidence of lymphocyte chromosomal aberrations was found in these glycerine-exposed workers as compared to workers not exposed to glycerine (Barna-Lloyd et al., 1979). However, no definitive conclusion could be drawn due to limitations of the study design, statistical methods used, group organization, and culture medium preparation.

Thus, under the category of structural chromosomal aberrations it is recommended that an assay with 1,3-dichloropropene be performed.

Under the category of tests for other genotoxic effects, Sudo et al. (1978) demonstrated that DNA damage was found with 1,3-dichloropropene (mixture of cis and trans isomers, 96.1%) at 25 mg/ml in a non-activated recombination assay using B. subtilis M 45 and H 17 strains. At this time, no further testing relative to DNA damage/repair is requested.

It is concluded that 1,3-dichloropropene (mixture of cis and trans isomers) induces gene mutation and DNA damage in procaryotic cells. In these systems, 1,3-dichloropropene is a direct acting mutagen not requiring metabolic activation to induce mutagenic effects.

METABOLISM

Two metabolism studies are presently available. Hutson et al. (1971) investigated the metabolic fate of radioactive [C^{14}] cis and trans 1,3-dichloropropene (>99% purified) after oral administration in rats. The amounts of radioactivity excreted in the urine and feces were monitored daily. After 4 days, all animals were sacrificed and the radioactivity level in the skin, gastrointestinal tract, and carcass was determined. Elimination of the radiolabel by pulmonary excretion was also monitored. The urine apparently was the major route of excretion for both isomers and accounted for 80% and approximately 60% of the administered dose for cis- and trans-1,3-dichloropropene, respectively. Over 90% of the administered dose was recovered after 4 days. The levels of both isomers were almost non-existent in the gastrointestinal tract, skin, and carcass. When the amount of radiolabel was monitored for pulmonary excretion, the trans isomer yielded 23.1% whereas only 3.9% of the administered dose was obtained from the cis isomer. In this study, determination of possible metabolites in the urine and feces was not conducted and kinetic data could not be calculated in the absence of plasma concentration.

A metabolism study using the cis-dichloropropene isomer was conducted by Climie and Morrison (1978). Radioactive material was given as a single oral dose to two female Wistar rats. Urine and feces were collected for 2 days and the metabolites quantified and identified. The main metabolite was identified as methyl-N-acetyl-S-[(Z)-3-chloroprop-2-enyl] cysteine. In-vitro studies with the cis-isomer incubated with rat liver cytosol and glutathione (Climie and Morrison, 1978) revealed the presence of S-[(Z)-3-chloroprop-2-enyl] glutathione. These findings suggest that cis-1,3-dichloropropene was biotransformed by a glutathione-dependent system, at least in the rat. The intermediate glutathione conjugate once formed may undergo mercapturic acid biotransformation to yield the main metabolite found in urine. Therefore, formation of polar metabolites through both the glutathione and mercapturic acid pathways appears as detoxifying mechanisms for cis-1,3-dichloropropene in the rat. Determination of radioactive material in different organs was not undertaken in this study (Climie and Morrison, 1978).

These two studies collectively still do not fulfill the regulatory requirements for a metabolism study. Bioavailability data, plasma half-life, pharmacokinetic data, and concentrations of 1,3-dichloropropene in organs other than the skin, gastrointestinal tract, and carcass are presently not available.

TOXICOLOGY DATA GAPS

1. Acute Toxicity

The rabbit dermal LD50 and rat inhalation LC50 are classified as Core Supplementary Data and are considered as data gaps. Further, no dermal sensitization studies are available.

2. Subchronic Toxicity

The 90-day inhalation and feeding studies with Telone were classified as Core Supplementary Data and are considered as data gaps.

3. Chronic Toxicity

The two NTP carcinogenicity assays with Telone II (1% epichlorohydrin) in rats and mice do not fulfill the regulatory requirements for chronic toxicity studies since both studies were not specifically designed to investigate the long term effects of Telone II. Further, these two studies could not be used for the registration of the new Telone formula in which the stabilizer epichlorohydrin has been replaced by epoxidized soybean oil. The registrant indicated that chronic inhalation studies with the new formula in rats and rabbits are in progress and final reports are expected in 1988. At this time, data gaps exist for chronic toxicity testing in two species.

The Residue Chemistry Branch section of this Registration Standard indicates that residues of Telone II may be taken up by plants and, hence, the present nonfood determination is not appropriate. Although at the present time, no tolerances or exemptions from tolerances for residues of Telone in or on food/feed commodities exist, an appropriate tolerance definition (1,3-dichloropropene and metabolites) must be established along with tolerances for residues in or on all food crops on which use of Telone is registered. In such case, chronic toxicity studies by the oral route must also be performed.

4. Oncogenicity

NTP conducted two carcinogenicity assays with Telone II (1% epichlorohydrin) in rats and mice. The rat study is classified as Core Minimum Data whereas a classification of Core Supplementary Data is assigned to the mouse study. However, the registrant has recently (2/25/85) submitted a new formula for Telone II in which epichlorohydrin is replaced by epoxidized soybean oil. Therefore, to fully assess the oncogenic potential of the newly submitted Telone formula, it is recommended that oncogenicity studies must be conducted in two species with this new formula. Further, as pointed out by Residue Chemistry Branch, a tolerance may need to be established for Telone in or on all food crops. Consequently oncogenicity studies with the new formula in the diet will be necessary.

5. Teratogenicity

Both inhalation teratology studies with Telone II (1% epichlorohydrin) in rats and rabbits are classified as Core Supplementary Data. Evidence of teratogenicity was not apparent in both species. However, conclusions relative to developmental toxicity (embryo/fetotoxicity) must await the submission of requested available additional data. Both studies may potentially be upgraded pending the submission and adequacy of the requested data. However, if tolerances are found to be necessary for Telone in or on the food crops for which Telone is registered, then teratology studies using the oral route of exposure must also be considered.

6. Reproduction

A reproduction study with Telone II is presently lacking. The registrant indicated that an inhalation two generation reproduction study with the new Telone formulation will be initiated in 1985 with the final report issued in 1987. Investigation using the oral route should also be considered if tolerances are found necessary for Telone in or on the food crops for which Telone is registered.

7. Mutagenicity

At the present time, the registrant has fulfilled the requirements for the category of tests for (1) gene mutation and (2) other mutagenic mechanisms, including DNA damage/repair. However, it is recommended that an assay be performed for the category of structural chromosomal aberrations.

8. Metabolism

The registrant has not fulfilled the regulatory requirements for a metabolism study.

TELONE II®
92% 1,3 Dichloropropene

005537

Toxicology - Acute Oral Toxicity, Rat and Mouse 81:1

CHEMICAL-- Telone II

PAGE 1 of __ for this requirement::DATED __/__/__::Supercedes page dated __/__/__

Current Use	Use Category	Guideline Status	Are Data Required	Footnote Number
☐	A. Terrestrial - Food Crop	[R]		
☒	B. Terrestrial - Nonfood	[R]	R	
☐	C. Aquatic - Food Crop	[R]		
☐	D. Aquatic - Nonfood	[R]		
☐	E. Greenhouse - Food Crop	[R]		
☐	F. Greenhouse - Nonfood	[R]		
☐	G. Forestry	[R]		
☒	H. Domestic Outdoor	[R]	R	
☐	I. Indoor	[R]		

STATUS OF DATA REQUIREMENTS

Satisfied ✓ Partially Satisfied _____ Not Satisfied _____

Months to Generate Additional Data _____

CITATIONS: (S= Fully satisfactory P= Partially Satisfactory N= Not Useful)

MRID # 00039686 : S

MRID # 00039683 : S

DATA REQUIREMENT FOOTNOTES:

005537

Toxicology - Acute Dermal Toxicity *Rabbit* 81:2

CHEMICAL-- *Telone II*

PAGE 1 of __ for this requirement::DATED __/__/__::Supercedes page dated __/__/__

Current Use	Use Category	Guideline Status	Are Data Required	Footnote Number
☐	A. Terrestrial - Food Crop	[R]		
☒	B. Terrestrial - Nonfood	[R]	R	
☐	C. Aquatic - Food Crop	[R]		
☐	D. Aquatic - Nonfood	[R]		
☐	E. Greenhouse - Food Crop	[R]		
☐	F. Greenhouse - Nonfood	[R]		
☐	G. Forestry	[R]		
☒	H. Domestic Outdoor	[R]	R	
☐	I. Indoor	[R]		

STATUS OF DATA REQUIREMENTS

Satisfied _____ Partially Satisfied _____ Not Satisfied ✓

Months to Generate Additional Data _____

CITATIONS: (S= Fully satisfactory P= Partially Satisfactory N= Not Useful)

MRID # 000 39676 : N (Supplementary data)

DATA REQUIREMENT FOOTNOTES:

005537

Toxicology - Acute Inhalation Toxicity - rat 81:3

CHEMICAL-- *Telone II*

PAGE 1 of __ for this requirement::DATED __/__/__::Supercedes page dated __/__/__

Current Use	Use Category	Guideline Status	Are Data Required	Footnote Number
☐	A. Terrestrial - Food Crop	[R]		
☒	B. Terrestrial - Nonfood	[R]	R	
☐	C. Aquatic - Food Crop	[R]		
☐	D. Aquatic - Nonfood	[R]		
☐	E. Greenhouse - Food Crop	[R]		
☐	F. Greenhouse - Nonfood	[R]		
☐	G. Forestry			
☒	H. Domestic Outdoor	[R]	R	
☐	I. Indoor	[R]		

STATUS OF DATA REQUIREMENTS

Satisfied _____ Partially Satisfied _____ Not Satisfied ✓

Months to Generate Additional Data _____

CITATIONS: (S= Fully satisfactory P= Partially Satisfactory N= Not Useful)

MRID # 00032985 : N (Supplementary Data)

DATA REQUIREMENT FOOTNOTES:

005537

Toxicology - Primary eye irritation - rabbit 81:4

CHEMICAL-- Telone II

PAGE 1 of __ for this requirement: DATED __/__/__ : Supercedes page dated __/__/__

Current Use	Use Category	Guideline Status	Are Data Required	Footnote Number
☐	A. Terrestrial - Food Crop	[R]		
☒	B. Terrestrial - Nonfood	[R]	R	
☐	C. Aquatic - Food Crop	[R]		
☐	D. Aquatic - Nonfood	[R]		
☐	E. Greenhouse - Food Crop	[R]		
☐	F. Greenhouse - Nonfood	[R]		
☐	G. Forestry	[R]		
☒	H. Domestic Outdoor	[R]	R	
☐	I. Indoor	[R]		

STATUS OF DATA REQUIREMENTS

Satisfied ✓ Partially Satisfied _____ Not Satisfied _____

Months to Generate Additional Data _____

CITATIONS: (S= Fully satisfactory P= Partially Satisfactory N= Not Useful)

MRID # 00039676 . S

DATA REQUIREMENT FOOTNOTES:

005537

Toxicology - Primary dermal irritation - Rabbit 81:5

CHEMICAL-- Telone II

PAGE 1 of __ for this requirement::DATED __/__/__::Supercedes page dated __/__/__

Current Use	Use Category	Guideline Status	Are Data Required	Footnote Number
[ ]	A. Terrestrial - Food Crop	[R]		
[X]	B. Terrestrial - Nonfood	[R]	R	
[ ]	C. Aquatic - Food Crop	[R]		
[ ]	D. Aquatic - Nonfood	[R]		
[ ]	E. Greenhouse - Food Crop	[R]		
[ ]	F. Greenhouse - Nonfood	[R]		
[ ]	G. Forestry	[R]		
[X]	H. Domestic Outdoor	[R]	R	
[ ]	I. Indoor	[R]		

STATUS OF DATA REQUIREMENTS

Satisfied ✓ Partially Satisfied _____ Not Satisfied _____

Months to Generate Additional Data _____

CITATIONS: (S= Fully satisfactory P= Partially Satisfactory N= Not Useful):

MRID # 00039676 . S

DATA REQUIREMENT FOOTNOTES:

005537

Toxicology - Dermal sensitization - Guinea Pig 005537 81:6

CHEMICAL-- Telone II

PAGE 1 of __ for this requirement::DATED __/__/__::Supercedes page dated __/__/__

Current Use	Use Category	Guideline Status	Are Data Required	Footnote Number
[ ]	A. Terrestrial - Food Crop	[R]		
[X]	B. Terrestrial - Nonfood	[R]	R	
[ ]	C. Aquatic - Food Crop	[R]		
[ ]	D. Aquatic - Nonfood	[R]		
[ ]	E. Greenhouse - Food Crop	[R]		
[ ]	F. Greenhouse - Nonfood	[R]		
[ ]	G. Forestry	[R]		
[X]	H. Domestic Outdoor	[R]	R	
[ ]	I. Indoor	[R]		

STATUS OF DATA REQUIREMENTS

Satisfied _____ Partially Satisfied _____ Not Satisfied ✓

Months to Generate Additional Data _____

CITATIONS: (S= Fully satisfactory P= Partially Satisfactory N= Not Usefui)

No data

DATA REQUIREMENT FOOTNOTES:

005537

Toxicology - Acute delayed neurotoxicity - hen 81:7

CHEMICAL-- Telone II

PAGE 1 of __ for this requirement::DATED __/__/__::Supercedes page dated __/__/__

Current Use	Use Category	Guideline Status	Are Data Required	Footnote Number
[ ]	A. Terrestrial - Food Crop	[R]		
[X]	B. Terrestrial - Nonfood	[R]	No	
[ ]	C. Aquatic - Food Crop	[R]		
[ ]	D. Aquatic - Nonfood	[R]		
[ ]	E. Greenhouse - Food Crop	[R]		
[ ]	F. Greenhouse - Nonfood	[R]		
[ ]	G. Forestry	[R]		
[X]	H. Domestic Outdoor	[R]	No	
[ ]	I. Indoor	[R]		

STATUS OF DATA REQUIREMENTS

Satisfied _____ Partially Satisfied _____ Not Satisfied _____

Months to Generate Additional Data _____

CITATIONS: (S= Fully satisfactory P= Partially Satisfactory N= Not Useful)

DATA REQUIREMENT FOOTNOTES:

Telone is not an organophosphate and is not structurally related to a substance that causes delayed neurotoxicity

005537

:Toxicology - 90-day feeding - rodent, non-rodent 82:1

:CHEMICAL-- *Telone II*

:PAGE 1 of __ for this requirement::DATED __/__/__::Supercedes page dated __/__/__:

Current Use	Use Category	Guideline Status	Are Data Required	Footnote Number
☐	A. Terrestrial - Food Crop	[R]		
☒	B. Terrestrial - Nonfood		R	(1)
☐	C. Aquatic - Food Crop	[R]		
☐	D. Aquatic - Nonfood			
☐	E. Greenhouse - Food Crop	[R]		
☐	F. Greenhouse - Nonfood			
☐	G. Forestry			
☒	H. Domestic Outdoor		R	
☐	I. Indoor	[R]		

:STATUS OF DATA REQUIREMENTS (2)

Satisfied _____ Partially Satisfied _____ Not Satisfied ✓

Months to Generate Additional Data _____

:CITATIONS: (S= Fully satisfactory P= Partially Satisfactory N= Not Useful):

MRID # 00067977 and 000 39684 : N (Supplementary data)

DATA REQUIREMENT FOOTNOTES:

(1) Intended uses of the product may result in residues in food crop

(2) Not required if chronic feeding data are available ~~(studies in progress)~~

005537

Toxicology - 21-day dermal 82:2

CHEMICAL-- Telone II

PAGE 1 of __ for this requirement: DATED __/__/__ : Supercedes page dated __/__/__

Current Use	Use Category	Guideline Status	Are Data Required	Footnote Number
[ ]	A. Terrestrial - Food Crop	[CR]		
[X]	B. Terrestrial - Nonfood	[CR]	R	*
[ ]	C. Aquatic - Food Crop	[CR]		
[ ]	D. Aquatic - Nonfood	[CR]		
[ ]	E. Greenhouse - Food Crop	[CR]		
[ ]	F. Greenhouse - Nonfood	[CR]		
[ ]	G. Forestry	[CR]		
[X]	H. Domestic Outdoor	[CR]	R	
[ ]	I. Indoor	[CR]		

STATUS OF DATA REQUIREMENTS

Satisfied _____ Partially Satisfied _____ Not Satisfied ✓

Months to Generate Additional Data _____

CITATIONS: (S= Fully satisfactory P= Partially Satisfactory N= Not Useful)

No data

DATA REQUIREMENT FOOTNOTES:

* Human exposure may be via skin contact

R Repeated

005537

005537

Toxicology - 90-day dermal 82:3

CHEMICAL-- Telone II

PAGE 1 of ___ for this requirement::DATED __/__/__::Supercedes page dated __/__/__

Current Use	Use Category	Guideline Status	Are Data Required	Footnote Number
[ ]	A. Terrestrial - Food Crop	[CR]		
[X]	B. Terrestrial - Nonfood	[CR]	No	
[ ]	C. Aquatic - Food Crop	[CR]		
[ ]	D. Aquatic - Nonfood	[CR]		
[ ]	E. Greenhouse - Food Crop	[CR]		
[ ]	F. Greenhouse - Nonfood	[CR]		
[ ]	G. Forestry	[CR]		
[X]	H. Domestic Outdoor	[CR]	No	
[ ]	I. Indoor	[CR]		

STATUS OF DATA REQUIREMENTS

Satisfied _____ Partially Satisfied _____ Not Satisfied _____

Months to Generate Additional Data _____

CITATIONS: (S= Fully satisfactory P= Partially Satisfactory N= Not Useful)

DATA REQUIREMENT FOOTNOTES:

005537

Toxicology - 90-day inhalation - rat 82:4

CHEMICAL-- Telone II

PAGE 1 of __ for this requirement::DATED __/__/__::Supercedes page dated __/__/__

Current Use	Use Category	Guideline Status	Are Data Required	Footnote Number
[ ]	A. Terrestrial - Food Crop	[CR]		
[X]	B. Terrestrial - Nonfood	[CR]	R	
[ ]	C. Aquatic - Food Crop	[CR]		
[ ]	D. Aquatic - Nonfood	[CR]		
[ ]	E. Greenhouse - Food Crop	[CR]		
[ ]	F. Greenhouse - Nonfood	[CR]		
[ ]	G. Forestry	[CR]		
[X]	H. Domestic Outdoor	[CR]	R	
[ ]	I. Indoor	[CR]		

STATUS OF DATA REQUIREMENTS (1)

Satisfied _____ Partially Satisfied _____ Not Satisfied ✓

Months to Generate Additional Data _____

CITATIONS: (S= Fully satisfactory P= Partially Satisfactory N= Not Useful):

MRID # 00119191 : N (Supplementary data)

MRID # 00117055 : N (Supplementary data)

MRID # 00039686 : N (Supplementary data)

DATA REQUIREMENT FOOTNOTES:

(1) Not required if chronic ~~inhalation~~ inhalation data will be submitted (studies in progress)

005537

Toxicology - 90-day neurotoxicity - hen and/or mammal 82:5

CHEMICAL-- *Telone II*

PAGE 1 of __ for this requirement::DATED __/__/__::Supercedes page dated __/__/__

Current Use	Use Category	Guideline Status	Are Data Required	Footnote Number
☐	A. Terrestrial - Food Crop	[CR]		
☒	B. Terrestrial - Nonfood	[CR]	*No*	*
☐	C. Aquatic - Food Crop	[CR]		
☐	D. Aquatic - Nonfood	[CR]		
☐	E. Greenhouse - Food Crop	[CR]		
☐	F. Greenhouse - Nonfood	[CR]		
☐	G. Forestry	[CR]		
☒	H. Domestic Outdoor	[CR]	*No*	
☐	I. Indoor	[CR]		

STATUS OF DATA REQUIREMENTS

Satisfied _____ Partially Satisfied _____ Not Satisfied _____

Months to Generate Additional Data _____

CITATIONS: (S= Fully satisfactory P= Partially Satisfactory N= Not Useful)

DATA REQUIREMENT FOOTNOTES:

* *Neuropathy / neurotoxicity not observed in acute oral, dermal, or inhalation studies*

Telone is not an organophosphate, carbamate, or structurally related to an agent that causes neurotoxicity

Toxicology -Chronic feeding - 2 spp. rodent and nonrodent 005537 3:1

CHEMICAL-- *Telone II*

PAGE 1 of __ for this requirement::DATED __/__/__::Supercedes page dated __/__/__

Current Use	Use Category	Guideline Status	Are Data Required	Footnote Number
[ ]	A. Terrestrial - Food Crop	[R]		
[X]	B. Terrestrial - Nonfood	[CR]	R	1, 2, 3
[ ]	C. Aquatic - Food Crop	[R]		
[ ]	D. Aquatic - Nonfood	[CR]		
[ ]	E. Greenhouse - Food Crop	[R]		
[ ]	F. Greenhouse - Nonfood	[CR]		
[ ]	G. Forestry	[CR]		
[X]	H. Domestic Outdoor	[CR]	R	1, 2, 3
[ ]	I. Indoor	[CR]		

STATUS OF DATA REQUIREMENTS

Satisfied _____ Partially Satisfied _____ Not Satisfied ✓

Months to Generate Additional Data _____

CITATIONS: (S= Fully satisfactory P= Partially Satisfactory N= Not Useful)

NTP-TR-269 (Publication # 84-2525) - rat - N (Supplementary data)

DATA REQUIREMENT FOOTNOTES:

1. *Intended uses may result in residues in food crop*
2. *Telone is a substance that causes mutagenic effects*
3. *Positive carcinogenic findings in rats and mice (NTP-TR-29)*

005537

Toxicology - Oncogenicity study - 2 spp. rat and mouse preferred 83:2

CHEMICAL-- *Telone II*

PAGE 1 of __ for this requirement::DATED __/__/__::Supercedes page dated __/__/__

Current Use	Use Category	Guideline Status	Are Data Required	Footnote Number
[ ]	A. Terrestrial - Food Crop	[R]		
[X]	B. Terrestrial - Nonfood	[CR]	R	1, 2
[ ]	C. Aquatic - Food Crop	[R]		
[ ]	D. Aquatic - Nonfood	[CR]		
[ ]	E. Greenhouse - Food Crop	[R]		
[ ]	F. Greenhouse - Nonfood	[CR]		
[ ]	G. Forestry	[CR]		
[X]	H. Domestic Outdoor	[CR]	R	1, 2
[ ]	I. Indoor	[CR]		

STATUS OF DATA REQUIREMENTS

Satisfied _____ Partially Satisfied ✓ Not Satisfied _____

Months to Generate Additional Data _____

CITATIONS: (S= Fully satisfactory P= Partially Satisfactory N= Not Useful):

NTP-TR- 269 (Publication No. 84-2525) - rat: S

NTP- TR - 269 (Publication No. 84 - 2525) - mouse : ~~S~~ N

(Supplementary data)

DATA REQUIREMENT FOOTNOTES:

1. *Positive mutagenic findings*
2. *Positive carcinogenic findings*

005537

Toxicology - Teratogenicity - 2 species 83:3

CHEMICAL-- Telone II

PAGE 1 of __ for this requirement::DATED __/__/__::Supercedes page dated __/__/__

Current Use	Use Category	Guideline Status	Are Data Required	Footnote Number
☐	A. Terrestrial - Food Crop	[R]		
☒	B. Terrestrial - Nonfood	[CR]	R	
☐	C. Aquatic - Food Crop	[R]		
☐	D. Aquatic - Nonfood	[CR]		
☐	E. Greenhouse - Food Crop	[R]		
☐	F. Greenhouse - Nonfood	[CR]		
☐	G. Forestry	[CR]		
☒	H. Domestic Outdoor	[CR]	R	
☐	I. Indoor	[CR]		

STATUS OF DATA REQUIREMENTS

Satisfied _____ Partially Satisfied _____ Not Satisfied ✓

Months to Generate Additional Data _____

CITATIONS: (S= Fully satisfactory P= Partially Satisfactory N= Not Useful)

~~None~~

Dow Chemical # HET M-003993-006 ; 10/31/83

inhalation-rat : N (Supplementary data)

inhalation-rabbit : N (Supplementary data)

DATA REQUIREMENT FOOTNOTES:

If residues of 1,3-dichloropropene are found in feed/food commodities, teratology studies using the feeding route of administration must also be required

Toxicology - Reproduction - 2 generation 005537 83:4

CHEMICAL-- *Telone II*

PAGE 1 of ___ for this requirement::DATED __/__/__::Supercedes page dated __/__/__

Current Use	Use Category	Guideline Status	Are Data Required	Footnote Number
[ ]	A. Terrestrial - Food Crop	[R]		
[X]	B. Terrestrial - Nonfood	[CR]	R	
[ ]	C. Aquatic - Food Crop	[R]		
[ ]	D. Aquatic - Nonfood	[CR]		
[ ]	E. Greenhouse - Food Crop	[R]		
[ ]	F. Greenhouse - Nonfood	[CR]		
[ ]	G. Forestry	[CR]		
[X]	H. Domestic Outdoor	[CR]	R	
[ ]	I. Indoor	[CR]		

STATUS OF DATA REQUIREMENTS

Satisfied _____ Partially Satisfied _____ Not Satisfied ✓

Months to Generate Additional Data _____

CITATIONS: (S= Fully satisfactory P= Partially Satisfactory N= Not Useful):

No data

DATA REQUIREMENT FOOTNOTES:

005537

Toxicology - Gene mutation 84:2

CHEMICAL-- Telone II

PAGE 1 of __ for this requirement::DATED __/__/__::Supercedes page dated __/__/__

Current Use	Use Category	Guideline Status	Are Data Required	Footnote Number
☐	A. Terrestrial - Food Crop	[R]		
☒	B. Terrestrial - Nonfood	[CR]	R	
☐	C. Aquatic - Food Crop	[R]		
☐	D. Aquatic - Nonfood	[CR]		
☐	E. Greenhouse - Food Crop	[R]		
☐	F. Greenhouse - Nonfood	[CR]		
☐	G. Forestry	[CR]		
☒	H. Domestic Outdoor	[CR]	R	
☐	I. Indoor	[CR]		

STATUS OF DATA REQUIREMENTS

Satisfied ✓ Partially Satisfied _____ Not Satisfied _____

Months to Generate Additional Data _____

CITATIONS: (S= Fully satisfactory P= Partially Satisfactory N= Not Useful)

MRID # 00120906 : S

00061059 : S

00039687 : S

00119179 : S

DATA REQUIREMENT FOOTNOTES:

005537

Toxicology - Chromosome aberration 84:2

CHEMICAL-- *Telone II*

PAGE 1 of __ for this requirement::DATED __/__/__::Supercedes page dated __/__/__

Current Use	Use Category	Guideline Status	Are Data Required	Footnote Number
[ ]	A. Terrestrial - Food Crop	[R]		
[X]	B. Terrestrial - Nonfood	[CR]	R	
[ ]	C. Aquatic - Food Crop	[R]		
[ ]	D. Aquatic - Nonfood	[CR]		
[ ]	E. Greenhouse - Food Crop	[R]		
[ ]	F. Greenhouse - Nonfood	[CR]		
[ ]	G. Forestry	[CR]		
[X]	H. Domestic Outdoor	[CR]	R	
[ ]	I. Indoor	[CR]		

STATUS OF DATA REQUIREMENTS

Satisfied _____ Partially Satisfied _____ Not Satisfied ✓

Months to Generate Additional Data _____

CITATIONS: (S= Fully satisfactory P= Partially Satisfactory N= Not Useful):

No data

DATA REQUIREMENT FOOTNOTES:

005537

Toxicology - Other mechanisms of mutagenicity 005537 84:4

CHEMICAL-- Telone II

PAGE 1 of __ for this requirement::DATED __/__/__::Supercedes page dated __/__/__

Current Use	Use Category	Guideline Status	Are Data Required	Footnote Number
[ ]	A. Terrestrial - Food Crop	[R]		
[X]	B. Terrestrial - Nonfood	[CR]	R	
[ ]	C. Aquatic - Food Crop	[R]		
[ ]	D. Aquatic - Nonfood	[CR]		
[ ]	E. Greenhouse - Food Crop	[R]		
[ ]	F. Greenhouse - Nonfood	[CR]		
[ ]	G. Forestry	[CR]		
[X]	H. Domestic Outdoor	[CR]	R	
[ ]	I. Indoor	[CR]		

STATUS OF DATA REQUIREMENTS

Satisfied ✓ Partially Satisfied _____ Not Satisfied _____

Months to Generate Additional Data _____

CITATIONS: (S= Fully satisfactory P= Partially Satisfactory N= Not Useful)

MRID # 00039688 : S

DATA REQUIREMENT FOOTNOTES:

005537

:Toxicology - General metabolism 85:1

:CHEMICAL-- Telone II

:PAGE 1 of __ for this requirement::DATED __/__/__::Supercedes page dated __/__/__:

Current Use	Use Category	Guideline Status	Are Data Required	Footnote Number
[ ]	A. Terrestrial - Food Crop	[R]		
[X]	B. Terrestrial - Nonfood	[CR]	R	*
[ ]	C. Aquatic - Food Crop	[R]		
[ ]	D. Aquatic - Nonfood	[CR]		
[ ]	E. Greenhouse - Food Crop	[R]		
[ ]	F. Greenhouse - Nonfood	[CR]		
[ ]	G. Forestry	[CR]		
[X]	H. Domestic Outdoor	[CR]	R	
[ ]	I. Indoor	[CR]		

:STATUS OF DATA REQUIREMENTS

Satisfied _____ Partially Satisfied _____ Not Satisfied ✓

Months to Generate Additional Data _____

:CITATIONS: (S= Fully satisfactory P= Partially Satisfactory N= Not Useful):

MRID # 00032984 : N (Supplementary data)

00039690 : N (Supplementary data)

DATA REQUIREMENT FOOTNOTES:

* Oncogenicity and chronic studies are required

005537

005537 86:1

Toxicology - Domestic animal safety

CHEMICAL-- Telone II

PAGE 1 of __ for this requirement::DATED __/__/__::Supercedes page dated __/__/__

Current Use	Use Category	Guideline Status	Are Data Required	Footnote Number
[ ]	A. Terrestrial - Food Crop	[CR]		
[X]	B. Terrestrial - Nonfood	[CR]	No	
[ ]	C. Aquatic - Food Crop	[CR]		
[ ]	D. Aquatic - Nonfood	[CR]		
[ ]	E. Greenhouse - Food Crop			
[ ]	F. Greenhouse - Nonfood			
[ ]	G. Forestry	[CR]		
[X]	H. Domestic Outdoor	[CR]	No	
[ ]	I. Indoor			

STATUS OF DATA REQUIREMENTS

Satisfied _____ Partially Satisfied _____ Not Satisfied _____

Months to Generate Additional Data _____

CITATIONS: (S= Fully satisfactory P= Partially Satisfactory N= Not Useful)

DATA REQUIREMENT FOOTNOTES:

005537

:CHEMICAL-- Telone II

:PAGE 2 of __ for this requirement::DATED __/__/__::Supercedes page dated __/__/__:

DISCUSSION OF DATA:

1. Chronic toxicity

The registrant indicated that a chronic inhalation study in rats and rabbits is in progress. Final reports are expected in 1988. However, it should be noted that if residues of Telone are found in food/feed commodities, chronic feeding studies must be required

2. Reproduction

An inhalation 2-generation reproduction study in rats is in progress. Final report is expected in 1987

3. Teratology

Both inhalation teratology studies (rat and rabbits) are presently classified as Core Supplementary Data. However, they may potentially be upgraded pending the submission and adequacy of additional requested data

Oral (gavage) teratology studies may be required if residues of Telone are found in food/feed commodities

4. Subchronic feeding

Study may be upgraded pending the submission of additional requested data. Not required if chronic feeding data are available.

5. Subchronic inhalation

Not required if chronic inhalation data (study in progress) are acceptable

MRID

00061059 Brooks, T.M.; Dean, B.J.; Wright, A.S. et al. (1978) Toxicity Studies with Dichloropropenes: Mutation Studies with 1,3-D and cis-1,3-Dichloropropene and the Influence of Glutathione on the Mutagenicity of cis-1,3-Dichloropropene in Salmonella typhimurium; Group Research Report TLGR.00A1.78. (Unpublished study received Sep 5, 1978 under 201-119; prepared by Shell Research, Ltd., England, submitted by Shell Chemical Co., Washington, D.C.; CDL:235251-F)

00117055 Clark, D.; Blair, D.; Cassidy, S.; et al. (1980) D-D: A 10 Week
00103280 Inhalation study of Mating Behaviour, Fertility and Toxicity in
00039691 Male and Female Rats: Group Research Report TLGR.80.023. (Unpublished study received Sep 22, 1982 under 464-EX-63; prepared by Shell Research Ltd., Eng., submitted by Dow Chemical U.S.A., Midland, MI; CDL:248418-F)

00032984 Climie, I.J.G.; Morrison, B.J. (1978) Metabolism Studies on (cis-trans)-1,3-Dichloropropene in the Rat: Group Research Report TLGR.0101.78. (Unpublished study received Jun 25, 1980 under 464-511; prepared by Shell Research, Ltd., submitted by Dow Chemical U.S.A., Midland, Mich.; CDL:242723-A)

00039685 Coate, W.B.; Keenan, D.L.; Hardy, R.J.; et al. (1978) Final Report: Telone(R) II (Production Grade): Project No. 174-126. (Unpublished study received Jul 22, 1980 under 464-EX-63; prepared by Hazleton Laboratories America, Inc., submitted by Dow Chemical U.S.A., Midland, Mich.; CDL:099515-L)

00119191 Coate, W.; Keenan, D.; Hardy, R.; et al. (1979) 90-day Inhalation Toxicity study in Rats and Mice: Telone II: Project No. 174-127. Final rept. (Unpublished study received Aug 24, 1979 under 464-511; prepared by Hazleton Laboratories America, Inc., submitted by Dow Chemical U.S.A., Midland, MI; CDL:240893-A)

00032987 Coate, W.B.; Keenan, D.L.; Hardy, R.J. (1979) Final Report: Subacute Inhalation Toxicity Study in Mice and Rats: Project No. 776-132. (Unpublished study received Jun 25, 1980 under 464-511; prepared by Hazleton Laboratories America, Inc., submitted by Dow Chemical U.S.A., Midland, Mich.; CDL:242723-D)

00039689 Dean, B.J.; Hutson, D.H.; Wright, A.S.; et al. (1978) The Protective Action of Glutathione against the Bacterial Mutagenicity of cis-trans-1,3-Dichloropropene: TLP/33/78. (Unpublished study received Jul 22, 1980 under 464-EX-63; prepared by Shell Research, Ltd., submitted by Dow Chemical U.S.A., Midland, Mich.; CDL:099515-Q)

00119179 De Lorenzo, F.; Degl'Innocenti, S.; Ruocco, A.; et al. (1975) Mutagenicity of Pesticides Containing 1,3-Dichloropropene. (Unpublished study received Jun 15, 1977 under unknown admin. no.; prepared by Univ. of Naples, Italy, submitted by Dow Chemical U.S.A., Midland, MI; CDL:230634-B)

00039687 De Lorenzo, F.; Degl'Innocenti, S.; Ruocco, A.; et al. (1977) Mutagenicity of pesticides containing 1,3-Dichloropropene. Cancer Research 37(7/Jun):1915-1917. (Also In unpublished submission received Jul 22, 1980 under 464-EX-63; submitted by Dow Chemical U.S.A., Midland, Mich.; CDL:099515-O)

00039676 Dow Chemical U.S.A. (1978?) Summary of Human Safety Data. Summary of studies 099515-I and 099515-J. (Unpublished study received Jul 22, 1980 under 464-EX-63; CDL:099515-C)

00120906 Flessel, P. (1977) Letter sent to J. Wesolowski dated Apr 8, 1977: Mutagen testing program, mutagenic activity of Telone II in the Ames salmonella assay. (Unpublished study received Jun 15, 1977 under unknown admin. no.; prepared by California, Dept. of Health, submitted by Dow Chemical U.S.A., Midland, MI; CDL: 230634-A)
00067534

00039690 Hutson, D.H.; Moss, J.A.; Pickering, B.A. (1971) The excretion and retention of components of the soil fumigant D-D and their metabolites in the rat. Food and Cosmetics Toxicology 9(?): 677-680. (Also In unpublished submission received Jul 22, 1980 under 464-EX-63; submitted by Dow Chemical U.S.A., Midland, Mich.; CDL:099515-R)

00062959 Kitchen, D.N. (1980) Histopathologic Evaluation of Tissues and Organs from Beagle Dogs in a Two-Year Chronic Oral Toxicity Study; Project No. 1021. (Unpublished study received Nov 24, 1980 under 201-119; prepared by Hastpath Laboratories, Inc., submitted by Shell Chemical Co., Washington, D.C.; CDL:243919

00109290 Mennear, J.; Hingard, B.; Sullivan, D.; et al. (1978) Report to Shell Kagaku Kabushiki Kaisha: Two-year Chronic Oral Toxicity Study with D-D in Albino Rats; IBT No. 621-06001. (Unpublished study received Sep 5, 1978 under 201-119; prepared by Industrial Bio-Test Laboratories, Inc., submitted by Shell Chemical Co., Washington, DC; CDL:235250-F)
00061053

00117056 Parker, C.; Coate, W.; Voelker, R. (1982) Subchronic inhalation toxicity of 1,3-dichloropropene/1,2-dichloropropane (D-D) in mice and rats. Journal of Toxicology and Environmental Health 9:899-910. (Also In unpublished submission received Sep 22, 1982 under 464-EX-63; submitted by Dow Chemical U.S.A., Midland, MI; CDL:248418-G)

00061054 Phillips, B.M.; Mastalski, K. (1977) Report to Shell Kagaku Kabushiki Kaisha: Two-Year Chronic Oral Toxicity Study with D-D Compound in Beagle Dogs; IBT No. 651-06000. (Unpublished study received Sep 5, 1978 under 201-119; prepared by Industrial Bio-Test Laboratories, Inc., submitted by Shell Chemical Co., Washington, D.C.; CDL:235251-A)

00031560 Rosenblum, I.; Talley, M. (1979) Evaluation of Instrumental Behavioral Performance of Rhesus Monkeys after Acute Exposure to Telone II. (Unpublished study received Jan 15, 1980 under 464-511; prepared by Albany Medical College, Institute of Comparative and Human Toxicology, submitted by Dow Chemical U.S.A., Midland, Mich., CDL:241636-A).

00061050 Shirasu, Y.; Moriya, M.; Kato, K. (1976?) Mutagenicity Testing on D-D in Microbial Syetems. (Unpublished study received Aug 7, 1978 under 201-119; prepared by Institute of Environmental Toxicology) submitted by Shell Chemical Co., Washington, D.C.; CDL:235250-C)

00039688 Suno, S.; Nakazawa, M.; Nakazono, M.; et al. (1978) The Mutagenicity Test on 1,3-Dichloropropene in Bacteria Test System: Project No. NRI-7A-2819. (Unpublished study received Jul 22, 1980 under 464-EX-63; prepared by Nomura Sogo Research Institute, submitted by Dow Chemical U.S.A., Midland, Mich.; CDL:099515-P)

00039684 Til, H.P.; Spanjers, M.T.; Feron, V.J.; et al. (1973) Sub-chronic
00067577 (90-Day) Toxicity Study with Telone in Albino Rats: Rapport No. R 4902. Final rept. (Unpublished study received Jul 22, 1980 under 464-EX-63; prepared by Centreal Instituut voor Voedingsonderzock, submitted by Dow Chemical U.S.A., Midland, Mich.; CDL:099515-K)

00039686 Torkelson, T.R.; Oyen, F. (1977) The toxicity of 1,3-Dichloropropene as determined by repeated exposure of laboratory animals. American Industrial Hygiene Association Journal 38(7/May):217-223. (Also In unpublished submission received Jul 22, 1980 under 464-EX-63; submitted by Dow Chemical U.S.A., Midland, Mich.; CDL:099515-M).

00039683 Toyoshima, S.; Sato, R.; Sato, S. (1978) The Acute Toxicity Test on Telone II in Mice. (Unpublished study received Jul 22, 1980 under 464-EX-63; prepared by Keio Univ., Drug Chemistry Institute, Chemotherapy Div. and Japan Experimental Medical Research Institute Co., Ltd., submitted by Dow Chemical U.S.A., Midland, Mich.; CDL:099515-J)

00094723 Van Duuren, B.L.; Goldschmidt, B.M.; Loewengart, G.; et al. (1979)
00108740 Carcinogenicity of halogenated olefinic and aliphatic hydrocarbons in mice. Journal of the National Cancer Institute 63 (6):1433-1439. (Published study: CDL:246768-B)

00117052 Venable, J.; McClimans, C.; Flake, R.; et al. (1980) A fertility study of male employees engaged in the manufacture of glycerin. Journal of Occupational Medicine 22(2):87-91. (Also In unpublished submission received Sep 22, 1982 under 464-EX-63; submitted by Dow Chemical U.S.A., Midland, MI; CDL:248418-B)

Barna-Lloyd, T., Dabney, B. J., Daniel, R. L., Flake, R. E., McClimans, C. D. and Venable, J. R., 1979. Cytogenic findings from epoxy resins and glycerine employees. Unpublished study submitted by Dow Chemical Co., U.S.A.

John, J. A., Kloes, P. M., Clahoun, L. L., and Young J. T., 1893. Inhalation teratology study in Fischer 344 rats and New Zealand rabbits. Unpublished studies submitted by Dow Chemical Co., U.S.A.

National Toxicology Program, N.T.P. TR-269, N.I.H. Publication No. 84-2525, Board draft 6/22/1984. NTP Technical report on the carcinogenesis studies of Telone II. Submitted by Dow Chemical Co., U.S.A.

STUDY EVALUATION

005537

Study Title:	Sub-chronic (90 day) toxicity study with Telone in albino rats
EPA Registration No.:	MRID # 00067977 MRID # 00039684
Testing Facility:	Central Institute for Nutrition and Food Research Netherlands
Final Report No.:	R-4002
Final Report Date:	November 1973
Study Authors:	Til, HP et al.
Sponsor:	Submitted by Dow Chemical Co.
Test Material:	Telone, a mixture of: cis-1,3-dichloropropene 40.2% (w/w) trans-1,3-dichloropropene 38.3% (w/w)
Dose Levels:	0, 1, 3, 10, and 30 mg/kg/day 6 days/week for 13 weeks
Species:	Albino rats, Wistar strain

Background Information

This study was previously reviewed by Dr. W. Dykstra (memo of 2/13/78) who classified it as Core Minimum Data. However, Dr. Dyskstra indicated that "all results of individual rats in each group must be presented for evaluation" and "the number of animals used to calculate the reported mean values was unclear".

A re-review of this study was necessary for this registration standard.

PROCEDURES

A copy of the procedures that were followed is attached. Comments on the procedures employed are given as follows:

1. All data reported were tabulated and presented as means. Individual data are not available to confirm the findings.

2. Ten animals per sex were assigned to each group. At least, 20 animals per sex should have been used per group.

3. Food consumption was measured weekly during the first 4 weeks of the study and in weeks 11 and 12.

4. Individual necropsy and histopathologic findings are not available.

5. Hematologic determinations were carried out only at week 12. Measurements were not made at study initiation nor at an intermediate time during the investigation.

6. Clinical chemistry was determined at study termination and was restricted to SGPT, SGOT, and SAP. Determinations should be extended to other components of the blood (Ca++, K+, glucose, BUN, bilirubin, protein, cholesterol,...).

7. Urinalysis was conducted only at the termination of the testing period (week 13). It should be done, at least, at an intermediate time during the investigation.

RESULTS

1. Clinical Observations

The authors reported that "no abnormalities of condition or behaviour" were observed in any of the tested groups. There are no clinical data to substantiate the authors' statement.

2. Mortality

The investigators reported that three rats of different treated groups died during the first 4-weeks. The cause of death of all three was attributed to technical error (gavage). All three deaths were replaced by rats of the same sex and body weight.

From the submitted data, it is impossible for this reviewer to identify the dead animals, their sex and group. Further, the time of death and identification of the replaced animals could not be assessed. Necropsy data concerning the three dead animals to justify the cause of death was not available. The study authors further indicated that one female of the 3 mg/kg group died on week 10. Necropsy data, animal identification, and cause of death were not reported.

3. Food Consumption

A biological significance in food consumption was not evident between the control and treated groups during the first 4-weeks of the study and at weeks 11 and 12.

4. Body Weights

Tabulated data relative to absolute body weights were reported. Apparently, there was no statistical significance in body weights among the groups. However, the reported findings could not be verified in the absence of individual animal data.

5. Food Efficiency

Food efficiency was calculated only during the first 4-weeks of the study. No biological or statistical difference was found among the groups. The food efficiency of males and females in the 30 mg/kg group (highest dose tested) was respectively, 0.35 and 0.29 as compared to 0.37 and 0.31 of male and female controls, respectively.

6. Hematology

A significant increase in packed cell volume and hemoglobin concentration was found in the 3 mg/kg group. However, no dose response relationship was evident from the data submitted. The biological significance of this finding, hence, is of questionable importance. Hematologic determinations should also be conducted at study initiation.

7. Clinical Chemistry

No compound-related effects were evident from the submitted data with respect to SGPT, SGOT, and SAP determinations. Determinations should also be conducted at study initiation and extended to other components of the blood (Ca++, K+, glucose, BUN, bilirubin, protein, cholesterol,...).

8. Urinalysis

Urinalysis and microscopic examinations for urine casts did not reveal any evidence of compound-related effects.

9. Necropsy data

The authors stated that no abnormal findings were detected that could be attributed to Telone administration.

10. Organ Weights

Absolute organ weights were not reported. The authors indicated that the relative kidney weight was statistically increased in the 10 and 30 mg/kg males and in females of the 30 mg/kg dosage level. Significant increases in relative liver weight and significant decrease in relative brain weight were also observed in females of the 30 mg/kg group. However, consistent findings were not found in males treated with the same dosage level (30 mg/kg/day).

11. Histopathology

A tabulated summary of all histopathologic findings was reported. From these submitted data, there were no changes that could be attributed to Telone administration. The frequency and severity of the histopathologic changes were similar between the control and highest dose animals (30 mg/kg). For the intermediate dosage levels, histopathologic examinations were restricted to the liver and kidney. There were no individual histopathology data to confirm or verify the reported findings.

DISCUSSION/RECOMMENDATION

Under the conditions of this study, the only observable toxic effects were the increase in relative kidney weights observed in males of the 10 mg/kg group and both males and females of the 30 mg/kg group (highest dose tested). Significant increases in relative liver weight and decreases in relative brain weight were observed in 30 mg/kg females but not in males. The investigators stated that administration of Telone up to and including a dosage level of 30 mg/kg/day did not produce any adverse effects relative to body weight, food consumption, serum enzyme levels, urinalysis, and histopathologic findings. However, none of the reported data could be substantiated in the absence of individual data. Further, dead animals could not be identified from this study, nor could their time of death be determined. Replacements could not be verified. Although hematology, clinical chemistry, and urinalysis were performed at or near study termination, these parameters should be analyzed at least at an intermediate time during the investigation.

In the absence of supporting data, a systemic NOEL could not be established by this reviewer. Further, it is recommended that this study be classified as Core Supplementary Data. The registrant is requested to submit additional data (individual data) and to provide clarification relative to all issues listed under the "Procedures" section (page 2) of this review.

STUDY EVALUATION

Study Title:	The excretion and retention of components of the soil fumigant D-D and their metabolites in the rat.
EPA Identification No.:	MRID #00039690
Sponsor:	Submitted by Dow Chemical Co.
Testing Laboratory:	Shell Research Ltd., Kent, England
Study Number:	N/A
Study Date:	Published article Food Cosmet. Toxicol. Vol 9, pp 677-680, 1971
Study Authors:	Hutson, D.H., Moss, J.A. and Pickering, B.A.
Test Compound:	cis-1,3-dichloro [2-^{14}C] propene trans-1,3-dichloro [2-^{14}C] propene
Dosage Level:	[C^{14}] cis-1,3-DCP : 2.53 mg, 7.68 uC per animal [C^{14}] trans-1,3-DCP : 2.70 mg, 8.50 uC per animal
Test Animal:	Rats, Catworth Farm E strain

PROCEDURES

In this investigation, radioactive [C^{14}] cis and trans 1,3 dichloropropenes (> 99% purified) were administered orally to two groups consisting each of 6 animals per sex. Each compound was given as a solution in 0.5 ml arachis oil. The amounts of radioactivity excreted in the urine and feces were monitored daily. After 4 days, all animals were sacrificed and the radioactivity in the skin, gastrointestinal tract, and carcass was determined by a combustion technique. In addition, groups of 3 animals per sex each were also exposed to [C^{14}] cis- or trans-1,3-DCP. Elimination of the radiolable by pulmonary excretion was monitored in these two groups.

The authors indicated that all animals weighed approximately 200-250 gm at study initiation and were housed under controlled environmental conditions in metabolic cages with food (unspecified) and water ad libitum.

RESULTS

24 hours after oral administration, the concentration of radioactive cis-1,3-DCP amounted to approximately 80 and 4% in the urine and feces, respectively. 58% and 2% of the administered dose of radioactive trans-1,3-DCP were also collected in the urine and feces, respectively, after the same time period (24 hours).

The incidences of radioactive recoveries 4 days after oral administration in both males and females are summarized as follows:

Recovery of radioactivity (% of administered dose) in 4 days

	Urine	Feces	G.I.	Skin	Carcass	Exhaled	Total Recovered
cis 1,3-DCP	83.2	5.1	0.1	0.5	0.7	3.9	> 90%
trans 1,3-DCP	58.0	2.2	0.3	0.6	1.0	23.1	> 90%

DISCUSSION

The urine apparently was the major route of excretion for both isomers and accounted for 80% and approximately 60% of the administered dose for cis and trans 1,3-DCP*, respectively. Four days after the oral administration of radioactive materials, over 90% of the administered dose were recovered. The levels of both isomers were almost non-existent in the gastrointestinal tract, skin, and carcass. These findings suggest that both isomers do not accumulate in these tissues. However, one difference in metabolic pathway exists between the two isomers. When the amount of radiolable was monitored from pulmonary excretion as ^{14}C-CO_2, the trans isomer yielded 23.1% whereas only 3.9% of the administered dose was obtained from the cis isomer. The high radioactivity found in expired air with the trans isomer may explain the lower radioactive concentration collected in the urine.

RECOMMENDATION

It is recommended that this study be classified as Core Supplementary Data. This published article was not intended to fulfill the regulatory requirements for a metabolism study which requires the following additional data:

1. Determination of possible metabolites in urine and feces.
2. Determination of the rate of absorption by comparing data between the intravenous and oral route of administration. Only oral administration was performed in this study.
3. Nonlabeled should be given orally to a group of rats for at least 14 days.
4. Levels of radioactivity should also be determined in other organs (bone, brain, fat, gonads, heart, kidney, liver, muscle, spleen, ...)
5. Kinetic data could not be calculated in the absence of plasma concentration.

This study cannot be upgraded in light of the deficiencies listed above.

STUDY EVALUATION

Study Title: 30-day inhalation with Telone II in rats and mice

EPA Identification No.: MRID #00039685

Sponsor: Submitted by Dow Chemical Co.,

Testing Facility: Hazleton Lab. America

Study Number: 174-126

Study Date: 9/12/78

Study Authors: W.B. Coate et al.

Test Material: Telone® II vapor (production grade)

Species: Fischer 344 rats
CD-1 albino mice

Dose Levels: 0, 3, 10, and 30 ppm
6 hours/day, 5 days/week for 4 weeks

PROCEDURES

Test material:	Telone® II vapor (production grade)
Dose levels:	0, 3, 10, and 30 ppm
Exposure:	6 hours/day, 5 days/week for 4 weeks
Species:	Fischer 344 rats
	CD-1 albino mice

The procedures used are summarized as follows:

Groups of 10 rats (mice) per sex each were exposed to 0, 3, 10, or 30 ppm of Telone II vapor (production grade) for 6 hours/day, 5 days/week for a total of 20 exposures.

The animals were housed 5 per cage under controlled humidity, temperature, and light cycle with food and water ad libitum. Clinical observations were made daily and body weights were recorded at study initiation and weekly thereafter. At study termination, all animals were subjected to a complete necropsy. Histopathologic examinations were performed on selected tissues (lung, heart, kidneys, brain, liver, and gonads).

Throughout the study, the exposure chamber temperature and humidity were monitored. The mean chamber temperature was 74° and the mean relative humidity was 66%. Analytical determinations of the chamber concentrations were conducted 4 times per day and the collected samples analyzed by gas chromatographic methods.

RESULTS

1. Analytical Determinations

Target concentrations of 3, 10, and 30 ppm were intended in this study. Analytical determinations of the chamber concentrations were performed daily and resulted in overall mean concentrations of 3.81 ppm, 10.09 ppm, and 29.51 ppm for the 3, 10, and 30 ppm groups, respectively.

2. Clinical Observations and Mortality

A. Fischer 344 rats

No deaths occurred during the entire investigation. Brownish stains in the back and neck areas were found in 3, 4, and 5 females of the groups receiving 3, 10, and 30 ppm, respectively. The biological significance of this finding is unclear.

B. CD-1 mice

No deaths occurred during this study. Yellowish stains of the fur were observed in all males (10) and 5 females of the 30 ppm group. The biological significance of staining of the fur remains problematical.

3. Body Weights (grams)

	MALE RATS				FEMALE RATS			
	0ppm	3ppm	10ppm	30 ppm	0ppm	3ppm	10ppm	30 ppm
Study initiation	127	131	126	129	92	93	93	94
Study termination	209	215	202	216	142	137	135	139
Body weight gain †	82	84	76	87	50	44	42	45
% of control †		102	93	106		88	84	90
	MALE MICE				FEMALE MICE			
Study initiation	30.0	29.7	29.6	29.4	24.8	25.2	25.2	24.9
Study termination	38.1	37.9	38.5	37.1	29.7	29.5	31.1	28.4
Body weight gain †	8.1	8.2	8.9	7.7	4.9	4.3	5.9	3.5
% of control †		101	110	95		88	120	71

(†): Calculated by this reviewer

In the rats, no evidence of body weight depression was noted in the males. Although the body weight gains of females were slightly lower than those of controls, statistical differences were not attained.

The body weight gains of male mice were statistically comparable to those of the controls. A slight decrease was noted in the 30 ppm females but no statistical difference was attained.

4. Gross Necropsy

A. Fischer 344 rats

The incidences of enlarged peribronchial lymph nodes were increased in the 3 and 10 ppm males as compared to controls. Incidences of 1, 5, 6, and 2/10 animals were found in males of the 0, 3, 10, and 30 ppm groups, respectively. The increases noted in the 3 and 10 ppm males apparently were of questionable biological significance.

No apparent compound-related necropsy changes were observed in female rats.

B. CD-1 mice

No compound-related effects were evident from the data reported for both males and females.

5. Histopathologic Examinations

A. Fischer 344 rats

Pneumonitis, peribronchial lymphoid hyperplasia, and perivascular lymphoid hyperplasia were noted in the lungs of most control and treated males and females. These findings occurred at a similar frequency and severity between the control and treated groups.

Nonsuppurative pericholangitis of the liver was observed in 3, 1, 3, and 5 males and in 1, 1, 0, 1 females of the 0, 3, 10, and 30 ppm groups, respectively. In the absence of a dose-response relationship, the biological significance of these findings is questionable.

B. CD-1 mice

Peribronchial and perivascular lymphoid hyperplasia and focal pneumonitis occurred at a similar frequency and severity in the control and treated groups. Focal interstitial nephritis was not found in control males but was observed in 3, 3, and 1 males of the 3, 10, and 30 ppm groups, respectively. Respective incidences of 1, 2, 4, and 2 were observed in females. The biological significance of this finding in the kidneys is questionable in the absence of a dose-response relationship.

CONCLUSIONS/DISCUSSION

Rats and mice exposed to Telone II vapor for 6 hours/day, 5 days/week for 4 weeks for up to and including a concentration of 30 ppm did not exhibit any apparent compound related toxic manifestations. Significant changes in body weight gains, necropsy, or histopathologic examinations were not observed in treated rats and mice at any of the dosage levels tested (0, 3, 10, and 30 ppm).

Under the conditions of this study, the systemic NOEL for both rats and mice was determined to be 30 ppm (highest dose tested).

RECOMMENDATION

It is recommended that the 30-day inhalation study in rats and mice be classified as Core Minimum Data with a systemic NOEL established at 30 ppm for both species (highest dose tested).

STUDY EVALUATION

005537

Study Title: Mutagen Testing Program, Mutagenic Activity of Telone II in the Ames Salmonella Assay

EPA Identification No.: MRID # 00120906

Sponsor: Submitted by Dow Chemical Company

Testing Facility: Department of Health, State of California

Study Number: N/A

Study Date: 4/8/77
Letter from Peter Flessel to J. Wesolowski

Test Compound: Telone II® technical, a mixture of

cis 1,3-Dichloropropene	47%
trans 1,3-Dichloropropene	45%
epichlorohydrin	1%
"inert" ingredients	7%

DISCUSSION/RECOMMENDATION

The mutagenic activity of Telone II was tested in strains TA-1538, TA-1537, and TA-98 for frame-schift mutation, and TA-1535 and TA-100 for base-pair substitution. All assays were conducted with and without metabolic activation.

The study author summarized all findings in a letter format. Hence, information relative to this investigation for both procedures and results was very restricted. However, the author indicated that positive results was obtained with Telone II in strains TA-1535 and TA-100.

This study by itself cannot be accepted. However, in light of similar results observed in other mutagenicity studies with Telone in the same strains (TA1935 and TA-100), the data presented in this letter confirm the findings that Telone is a mutagen in microorganisms through base-pair substitution.

STUDY EVALUATION

Study Title: Toxicity studies with dichloropropenes: Mutation studies with 1,3-D and cis-1,3-dichloropropene and the influence of glutathione on the mutagenicity of cis-1,3-dichloropropene in Salmonella typhimurium.

EPA Identification No.: MRID # 00061059

Approved: [signature] 5-16-81

Sponsor: Submitted by Shell Company

Testing Facility: Tunstall Lab., Enyland

Study Number: TLGR.0081.78

Study Date: May, 1978

Study Director: E. Thorpe

Study Authors: Brooks, T.M., Dean, B.J. and Wright, A.S.

Test Materials: a) 1,3-Dichloropropene (DD95)("purified inhibited 1,3-D")

cis 1,3-dichloropropene	51.3%
trans 1,3-dichloropropene	43.7%
epichlorohydrin	0.6%

b) cis 1,3-dichloropropene, 99% purity

Solvent: Dimethylsulphoxide

Dose Levels: 20, 100, 500, and 2000 ug/plate

Species: Salmonella TA-1538, TA-98, TA-1535, and TA-100

PROCEDURES

The mutagenic potential of 1,3-D (a mixture of cis 1,3-dichloropropene 51.3%, trans 1,3-dichloropropene 43.7%, epichlorohydrin 0.6%) and cis 1,3-dichloropropene (cis-D; 99% purity) was investigated in different strains of Salmonella typhimurium for either frameshift (TA-1538 and TA-98) or base-pair substitution (TA-1535 and TA-100) mutation in the presence and absence of metabolic activation.

Both test materials were diluted with dimethylsulfoxide to provide different testing solutions. Twenty ul of each solution was mixed with 2 ml of molten top agar and 0.1 ml of an overnight bacterial culture in phosphate buffer. For activation studies, 0.5 ml of the S-9 mix was added to each overlay tube. The contents were then mixed and poured onto minimal agar plates (trace of histidine), incubated at 37°C for 3 days, and the number of revertant colonies counted. Plates incubated with solvent only (dimethylsulfoxide) served as controls. The concentrations of 1,3-D and cis-D used per plate were 20, 100, 500, and 2000 ug.

Positive control agents for both activation and non-activated assays were not investigated.

RESULTS

1. Assays with "purified inhibited 1,3-D" (DD 95)

Evidence of a mutagenic effect (at least 2-fold increase in the number of revertants as compared to controls, and presence of a dose-response effect) was not demonstrated in the strains used for frame-shift mutation (TA-1538 and TA-98) in both the presence and absence of metabolic activation. However, positive results were obtained with strains TA-1535 and TA-100 for base-pair substitution in both activated and non-activated assays. Incorporation of a rat liver microsomal enzyme apparently enhanced the mutagenic activity of 1,3-D as illustrated in the following table.

	Number of revertants per plate	
	Without S-9	With S-9
TA-1535		
0	5[a]	10
20 ug	6	16
100 ug	8	20
500 ug	14	35
2000 ug	9	42
TA-100		
0 ug	12	11
20 ug	3	26
100 ug	12	37
500 ug	6	59
2000 ug	29	65

TA-1538 and TA-98 the numbers of revertants in the treated plates were comparable to those of the solvent controls.

(a): Mean values of triplicate assays

In the absence of metabolic activation, the lowest concentration of 1,3-D that produced a positive mutagenic effect was 500 ug and 2000 ug for strains TA-

1535 and TA-100, respectively. However, when the S-9 fraction was added to the cultures, respective lowest concentrations per plate increasing the number of revertants over control by at least two-fold in a dose-related fashion were 100 ug and 20 ug.

2. Assays with cis-1,3-dichloropropene (cis-D, 99%)

Positive mutagenic activity was noted in strains TA-1535 and TA-100 in both presence and absence of metabolic activation. In both absence and presence of metabolic activation, the lowest concentration that produced a positive response in strains TA-1535 and TA-100 was 100 ug and 20 ug, respectively. In addition, evidence of a mutagenic effect was demonstrated in TA-98 at concentrations of 100 ug and above per plate in the absence of metabolic activation and at 2000 ug per plate in the presence of metabolic activation. Further, the reversion frequency of the cis 1,3-D isomer appeared to be considerably higher that than of 1,3-D.

Without activation	TA-1535	TA-100	TA-98
0 ug	13	11	6
20 ug	24	35	8
100 ug	72	112	15
500 ug	108	228	27
2000 ug	20†	422	39
With activation			
0 ug	14	20	14
20 ug	25	51	11
100 ug	86	133	16
500 ug	150	262	25
2000 ug	194	727	82

(†) cytotoxic effect

3. Influence of glutathione (5 mM) on the mutagenic activity of cis 1,3-D

Glutathione (5 mM) was incorporated to investigate the impact of this enzyme on the mutagenic activity of cis 1,3-D in strain TA-100.

The results are presented as follows:

	No glutathione	With glutathione
Without metabolic activation		
10 ug	0	0
25 ug	0	0
50 ug	0	0
100 ug	33[a]	0
250 ug	71	0
500 ug	132	4
With metabolic activation		
10 ug	7	6
25 ug	17	0
50 ug	24	1
100 ug	62	11
250 ug	118	33
500 ug	185	81

(a) Results are expressed as test revertants/plate minus spontaneous revertants

The authors concluded that cis-D (99%) induced a dose-related increase in the reverse mutation of TA-100 in both the presence and absence of metabolic activation. The addition of 5 mM of glutathione to the soft agar overlay eliminated the mutagenic activity of cis 1,3-D completely in the absence of metabolic activation and reduced the mutagenic activity in presence of metabolic activation.

DISCUSSION/RECOMMENDATION

Positive mutagenic responses were observed with "purified inhibited 1,3-D" (DD 95, a mixture of cis 1,3-dichloropropene 51.3%, trans 1,3-dichloropropene 43.7%, and epichlorohydrin 0.6%) in strains TA-1535 and TA-100 in both the presence and absence of metabolic activation. However, negative results were obtained from assays conducted with strains TA-1538 and TA-98. These findings suggest that this mixture is a mutagen at least in microorganisms by the induction of base-pair substitution. No evidence of frame-shift mutation was demonstrated from the data reported.

The isomer, cis 1,3-dichloropropene (99% purity) also induced mutagenic responses by base-pair substitution in both the presence and absence of metabolic activation. However, the mutagenic frequency induced by this isomer was considerably higher than that of the DD 95 mixture. With respect to frameshift mutation, positive results were found in strain TA-98 in both the presence and absence of metabolic activation. However, negative results were obtained with strain TA-1538 in both presence and absence of metabolic activation.

These findings, collectively, indicated that this cis-isomer probably was responsible for all mutagenic activities of 1,3-dichloropropene.

Addition of glutathione at 5 mM abolished the mutagenic effect of cis 1,3-D at least in the absence of metabolic activation and reduced its effectiveness in the presence of metabolic activation. Lowest concentrations of cis 1,3-D which induced a mutagenic response in strain TA-100 were 100 and 250 ug/plate in the absence and presence of glutathione, respectively. These findings suggested that glutathione apparently was involved in detoxifying cis 1,3-D and, hence, would offer some protection against the mutagenic action of this isomer as well as of 1,3-D mixture. The modifying activity of the glutathione system was confirmed by data (Tunstall Lab.# TLGR.0101.78) previously submitted and reviewed by the Agency (Dr. Bui's memo of 1/11/85)

It is recommended that this study be classified as Acceptable Data. There was sufficient evidence to indicate that the 1,3-D mixture (DD 95) is a mutagen by inducing base-pair substitution (TA-1535 and TA-100). One of its isomers, cis 1,3-dichloropropene (99% purity), also induced mutagenic responses through base-pair substitution (TA-1535 and TA-100) but in addition, frameshifts, as indicated by positive results in TA-98. These data suggest that both the DD 95 mixture and cis 1,3-dichloropropene may be direct mutagens since mutagenic response occurred without metabolic activation.

005537

STUDY EVALUATION

Study Title: Mutagenicity of pesticides containing 1,3 Dichloropropene

EPA Identification No.:

MRID # 00039687
MRID # 00119179

Approved: Greg Kramer 5-11-85

Testing Facility: University of Naples
Naples, Italy

Study Number: N/A

Study Date: Published article
Cancer Research, Vol. 37, 1915-1917, June 1977

Study Authors: De Lorenzo F., Deyl'Innoccenti S., Ruocco A., et al.,

Sponsor: Submitted by Dow Chemical Co.,

Test Compound: Telone, commercial product supplied by the Italian "Ministero della Sanita":

cis 1,3-Dichloropropene		30%
trans 1,3-Dichloropropene		30%
1,2-Dichloropropane		20%
2,3-Dichloro-1-propene		5%
Allyl chloride		2%
Unknown	about	15%

Dosage Levels: 0, 100 ug, 250 ug, 1 mg, 2.5 mg, 5 mg, and 10 mg per plate

Species: Salmonella TA 1978, TA 1535, TA 100, TA 1537, and TA 98

PROCEDURES

The potential of Telone to induce gene mutation was investigated in:

1. Salmonella TA 100 and TA 1535 for base pair substitution.
2. Salmonella TA 1978, TA 1537, and TA 98 for frame shift mutation.

Telone was diluted in dimethyl sulfoxide and aliquots containing different amounts of the test material were applied to the plates. The concentrations of Telone used were 0, 100 ug, 250 ug, 1 mg, 2.5 mg, 5 mg, and 10 mg per plate. The study authors indicated that the procedures for the assay as well as for the preparation of liver microsomal fractions followed those of Ames (1971) and McCann et al. (1975). However, no positive control agents were used for either activation or non-activation assays.

RESULTS

1. Bacterial Mutation Without Microsomal Activation

The results obtained are tabulated as follows:

	Number of mutant colonies/plate				
Dose levels	TA 1978	TA 1537	TA 98	TA 1535	TA 100
0	8	15	22	17	71
100 ug	24	25	28	12	178
250 ug	36	31	35	48	225
1.0 mg	45	18	27	75	263
2.5 mg	53	34	33	115	425
5.0 mg	61	27	24	150	282
10.0 mg	15	12	31	78	192

In the strains used to detect frame shift mutation, evidence of a positive mutagenic response (two-fold increase in the number of revertants per plate as compared to controls, and presence of a dose-related effect) was not demonstrated in strains TA-1537 and TA-98. However, positive mutagenic responses were noted in strain TA-1978. The investigators indicated that strain TA-1978 (provided by Dr. Ames) has the same histidine mutation as does TA-1538, but has a normal DNA-excision repair system.

Positive mutagenic responses were observed in the strains used to detect base-pair substitution. Dose-related increases in the number of revertants per plate were noted in both strains TA 1535 and TA 100. The decrease in the numbers of revertants observed at 10 mg/plate in both strains suggested that cytotoxicity was associated with this dosage level.

2. Bacterial Mutation With Metabolic Activation

The results obtained in microorganisms after treatment with Telone in the presence of metabolic activation are tabulated as follows:

Dose Levels	Number of mutant colonies/plate TA 1978	TA 1537	TA 98	TA 1535	TA 100
0	8	15	22	17	71
100 ug	115	23	32	15	151
250 ug	225	27	31	59	191
1.0 mg	249	19	36	90	242
2.5 mg	270	32	39	135	385
5.0 mg	365	25	40	220	500
10.0 mg	150	35	41	61	212

It should be noted that the number of spontaneous mutant colonies reported for all strains tested is identical in both activated and non-activated assays

Cytotoxicity was demonstrated in all strains tested at the 10 mg/plate dose level. Although negative results were still obtained in strains TA 1537 and TA 98, evidence of a positive mutagenic response was demonstrated in the presence of metabolic activation in strain TA 1978. The lowest dose concentration that produced a mutagenic response in TA 1978 was 100 ug/plate. In the strains that were used for base-pair substitution (TA-1535 and TA 100), positive results were obtained in both strains at 100 ug/plate.

3. Mutagenic Response of Each Component of Telone

The investigators also tested the mutagenic response of four components of Telone in strain TA-1978 for frame-shift mutation and in strains TA-1535 and TA-100 for base-pair substitution in the presence and absence of metabolic activation.

	Number of mutant colonies/plate					
	Without Metabolic Act.			With Metabolic Act.		
Dose levels	TA-1978	TA-1535	TA-100	TA-1978	TA-1535	TA-100
Control	25	19	87	28	21	89
Cis 1,3-Dichloropropene (30% of Telone)						
20 ug	19	248	594	21	77	731
50 ug	90	680	1800	71	490	2100
100 ug	119	1210	1750	131	990	1551
Trans 1,3-Dichloropropene (30% of Telone)						
20 ug	27	235	362	31	109	650
50 ug	68	430	1750	75	381	2200
100 ug	115	925	1820	91	828	1550
1,2-Dichloropropane (20% of Telone)						
10 ug	27	75	220	38	81	185
20 ug	38	210	480	21	185	450
50 ug	48	411	850	15	312	920
2,3-Dichloro-1-propene (5% of Telone)						
20 ug	31	190	531	51	212	450
50 ug	85	650	1520	97	451	1091
100 ug	98	1080	1900	81	875	1355

In strain TA-1978 (frame-shift mutation), positive mutagenic responses were observed with cis 1,3-dichloropropene, trans 1,3-dichloropropene, and 2,3-dichloro-1-propene with and without metabolic activation. The lowest concentration per plate that induced a positive effect for cis, trans 1,3-dichloropropene, and 2,3-dichloro-1-propene was 50 ug with or without metabolic activation. 1,2-dichloropropane did not exhibit any evidence of a mutagenic effect in TA-1978.

All four chemicals induced positive mutagenic effects in strains TA-1535 and TA-100 in the presence and absence of metabolic activation at all concentrations tested. The lowest positive concentration for cis and trans 1,3-dichloropropene and 2,3-dichloro-1-propene was 20 ug/plate and that for 1,2-dichloropropane was 10 ug/plate.

DISCUSSION/RECOMMENDATION

Information relative to the cytotoxic effect of Telone, background incidence of the strains used, culture preparation, procedures for metabolic activation, positive control, etc.,... was not available. However, from the limited data, it still can be concluded that the Telone commercial formula used in this study may be classified as a mutagen.

In the strains used to detect base-pair substitution (TA-1535 and TA-100), positive results were obtained in the presence and absence of metabolic activation. The lowest concentration of commercial Telone that produced a positive effect in these strains was 100 ug/plate (lowest concentration tested). Positive mutagenic responses were also noted in strain TA-1978 which was used to detect frame-shift mutation. The investigators stated that this strain was provided by Dr. Bruce Ames and has the same mutation as does TA-1538 except for the presence of a DNA-excision repair system. The lowest concentration of commercial Telone that produced a positive effect in strain TA-1978 was 100 ug for both absence and presence of metabolic activation. Negative results were noted in strains TA-1537 and TA-98 (frame-shift mutation) in both activated and non-activated assays.

The investigators indicated that the commercial Telone used in this investigation consisted of five known ingredients and 15% of unknown compound. All known ingredients were investigated for their mutagenic potential except for allyl chloride (2%) which was considered by the study authors as non-mutagenic. All four tested ingredients in the commercial Telone formulation (cis-1,3-dichloropropene; trans-1,3-dichloropropene; 2,3-dichloro-1-propene; and 1,2-dichloropropane) induced positive mutagenic responses in TA-1535 and TA-100 with or without metabolic activation. The lowest positive concentration for cis-1,3-dichloropropene, trans-1,3-dichloropropene, and 2,3-dichloro-1-propene was 20 ug/plate (lowest dose tested) and that for 1,2-dichloropropane was 10 ug/plate (lowest dose tested).

Positive mutagenic responses were observed with cis-1,3-dichloropropene, trans-1,3-dichloropropene, and 2,3-dichloropropene in strain TA-1978 (frame-shift mutation) with and without metabolic activation. The lowest concentration that induced a positive response was 50 ug per plate for all these three ingredients. The fourth ingredient in the commercial Telone formulation, 1,2-dichloropropane, failed to produce a positive mutagenic response in strain TA-1978.

These data collectively suggest that evidence of a mutagenic response for the commercial Telone formulation was observed in both strains that detect base-pair substitution (TA-100 and TA-1535) and frame-shift mutation (TA-1978) in the presence

and absence of metabolic activation. The lowest concentration of the commercial product that induced a positive effect was 100 ug per plate (lowest dose tested).

All four active ingredients in the commercial Telone formulation produced positive mutagenic effects in strains TA-1535 and TA-100 (base-pair substitution) in both presence and absence of metabolic activation. Also, a positive mutagenic response was observed in strain TA-1978 (frame-shift mutation) for at least three out of four ingredients tested. Only 1,2 dichloropropane failed to induce a positive effect in strain TA-1978 in both activated and non-activated assays.

It is recommended that the results presented in this study be classified as Acceptable Data. It is concluded that the commercial Telone product as well as four of its ingredients displayed positive mutagenic potential.

END