CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
HUMAN HEALTH ASSESSMENT BRANCH

SUMMARY OF TOXICOLOGY DATA
1,3-DICHLOROPROPENE (TELONE II)

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DATA GAP STATUS

Chronic toxicity, rat:	No data gap, possible adverse effects
Chronic toxicity, dog:	No data gap, possible adverse effects
Oncogenicity, rat:	No data gap, possible adverse effects
Oncogenicity, mouse:	No data gap, possible adverse effects
Reproduction, rat:	No data gap, no adverse effects
Developmental toxicity, rat:	No data gap, no adverse effects
Developmental toxicity, rabbit:	No data gap, no adverse effects
Gene mutation:	No data gap, possible adverse effects
Chromosome effects:	No data gap, no adverse effects
DNA damage:	No data gap, possible adverse effects
Neurotoxicity:	Hen neurotoxicity studies are not required at this time

Toxicology one-liners are attached.

All relevant record numbers indexed as July 1, 2015 were examined, including acute studies on technical active ingredient. This includes record numbers up to 291556 (Document No. 50046-0241), as well as relevant older records of the 900,000+ series. Aldous, 6/29/16.

In the 1-liners below: ** indicates an acceptable study, **Bold face** indicates a possible adverse effect, and ## indicates a study on file but not yet reviewed.

The original Summary was prepared by F. Martz. Revisions in 1987 to 1990 were by J. Gee. Subsequent revisions were by C. Aldous (latest update being Aug. 3, 2016).

See also "Guidance for the Reregistration of Pesticide Products (Reregistration Standard) Containing 1,3-Dichloropropene (Telone II) as the Active Ingredient," US EPA, 9/18/86, DPR Record # 050620. The position of EPA (1986) was that if significant residues were found, oral studies would be required in addition to existing inhalation studies. This appears to explain the presence of recent dietary chronic studies in rat, mouse, and dog, even though acceptable inhalation studies were previously performed in the rodents. Document No. 50046-116 contains a chapter from the 1997 U.S. EPA RED on 1,3-dichloropropene. Gee, 5/23/89, updated by Aldous, 4/23/96.

NOTE: The following symbols may be used in the Table of Contents which follows:
** = data adequately address FIFRA requirement
† = study(ies) flagged as "possible adverse effect"
(N/A) = study type not currently required

This record contains summaries of studies. Individual worksheets may be useful for detailed assessment.

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METABOLISM AND PHARMACOKINETICS

50046-052 113124 Waechter, J. M., K. A. Brzak, L. P. McCarty, M. A. LaPack, and P. J. Brownson, "1,3-Dichloropropene (Telone II Soil Fumigant) inhalation pharmacokinetics and metabolism in human volunteers," The Dow Chemical Company, Midland, MI, Feb. 12, 1992, Laboratory Study # M-003993-023. Six male volunteers were exposed by inhalation for 6 hours to 1 ppm of *cis*/*trans*-1,3-dichloropropene (1,3-D, Telone II Soil Fumigant), consisting of 50.6% *cis*-1,3-dichloropropene and 45.2% *trans*-1,3-dichloropropene. Investigators assessed concentrations of the above 2 isomers in exhaled air and blood during and after exposure, as well

as urinary excretion of two key conjugation products: *cis* and *trans* N-acetyl cysteine (NAC). The respiratory uptake was about 80% for both isomers (based on comparison of chamber air with exhaled air). There was a rapid "plateau" of concentrations of both isomers in exhaled air in most subjects during exposure, followed by a rapid decrease below detection after termination of exposure in most cases. Subjects absorbed estimated total amounts of 4.2 mg of *trans* and 4.6 mg of *cis* isomers. For technical reasons, only 5 subjects provided blood samples throughout the exposure and post-exposure period. Blood concentrations averaged about 0.7 ng/g for *cis* and about 1.3 ng/g for *trans* Telone, respectively, for most samplings during the exposure period. These levels were about twice the respective limits of detections for respective isomers. For the *cis* isomer, 3 subjects showed no systematic increase between the earlier samplings (10-minutes to 3-hrs) and the 6-hr sampling (end of exposure). The other 2 subjects had a 2- to 3-fold increase of *cis* isomer at 6 hrs compared to the first 3 hours. For the *trans* isomer, all subjects showed a 1.5- to 3-fold increase at 6 hrs compared to the first 3 hours. For both isomers, inter-subject differences were minor for 4 subjects for the first 3 treatment hours. One subject had mostly levels below quantification limits during the exposure phase. One subject had maximal (6-hr) blood levels of both isomers which were markedly higher (up to about 3x) compared to the other subjects, suggesting a meaningful inter-subject variation. Post-exposure blood concentrations in most subjects were generally below detection limits or were marginally quantifiable levels, with occasional detectable levels in some subjects for at least 4 hrs for one or both isomers. The subject with the highest concentrations of both isomers at the final treatment phase assessment still had detectable levels of both isomers 4 hrs into the recovery period. Total urinary elimination by assayed NAC's was quite variable: *cis*-1,3-NAC excretion varied from 2.3 to 5.8 mg, whereas the much lower amounts of *trans* -1,3-D-NAC ranged from 0.4 to 1.9 mg. About 44% of the mass of those conjugates is attributable to parent Telone. Thus, although the NAC conjugates constituted large portions of absorbed Telone II, particularly for the *cis* isomer, fate of much of absorbed Telone II was not addressed in this study. Initial phase half-lives for urinary excretion of *cis* and *trans* NAC's were 4.2 and 3.2 hrs, respectively. Terminal phase half-lives were 12.3 and 17.1 hrs, respectively. This report was first examined by J. Sanborn of the Worker Health and Safety Branch of DPR, whose review described study methodology and key findings. Sanborn noted that although the NAC's are suitable indicators of exposure at the relatively high levels tested, sensitivity of analysis at that time (1992) was insufficient to assess the much lower anticipated exposure levels of field workers and particularly of bystanders. Study is supplementary by design, clearly showing the usefulness of NAC metabolites at high dose levels in persons with fully-functioning GSH conjugation capacity. This subsequent review by C. Aldous (Jan. 6, 2015) contains additional discussion and a table.

50046-120 162473 Stott, W. T., J. R. Gilbert, R. J. McGuirk, K. A. Brzak, M. D. Dryzga, and M. J. Bartels, "Bioavailability of microencapsulated Telone*II Soil Fumigant in Fischer 344 rats", The Dow Chemical Co., Midland, 8/21/96. Laboratory Project Study ID # M-003993-027. Female rats received 25 mg/kg each of microencapsulated (Midwest Research Institute) and neat Telone by gavage in corn oil, prior to sampling the blood for cis and trans isomers over the course of an hour. ^{13}C-telone was used for the neat treatment, whereas the microencapsulated application used the common isotope (^{12}C-telone), allowing investigators to distinguish between modalities of exposure by subsequent mass spectrometry. Microencapsulated Telone was quite stable in corn oil, yet gave peak blood concentrations within minutes after gavage administration. Microencapsulated cis- or trans- 1,3-dichloropropene was absorbed as quickly or more quickly

than neat administrations of the same isomers. Urinary excretion half-lives were determined. Thus microencapsulation is a viable technique for oral administration. Aldous, 9/7/99 (no worksheet).

50046-111 161853 Exact duplicate of 50046-120 162473, above.

50046-026 057488 Stott, W. T., and P. E. Kastl, "Inhalation pharmacokinetics of Technical Grade 1,3-Dichloropropene in rats," The Dow Chemical Company, Midland, MI, Aug. 1, 1985. This unpublished report is virtually identical to the publication: *Toxicology and Applied Pharmacology* publication: Stott, W. T. and P. E. Kastl, "Inhalation pharmacokinetics of Technical Grade 1,3-Dichloropropene in rats," *Toxicology and Applied Pharmacology* 85, 332-341 (1986). Anesthetized male F344 rats were exposed to 1,3-dichloropropene, 92.1% purity (49.3% *cis* and 42.3% *trans*: Lot AGR 204046) by nose-only inhalation exposure at 30, 90, 300, or 900 ppm for 3 hrs for most experiments. Based on breathing rate, tidal volume, and measurements of dichloropropene (DCP) levels in air entering and leaving the head-only exposure space, estimated absorbed dose was 82% of inhaled DCP for 30 ppm exposure, and 62-65% for 90-900 ppm. For blood analysis of *cis* and *trans* DCP, investigators repeatedly sampled blood from indwelling jugular cannulae. At 30-90 ppm, blood levels at 1, 2, and 3 hours of exposure were constant, followed by rapid declines at the end of exposure (especially rapid for *cis* isomer). At 300 ppm and particularly at 900 ppm, blood levels rose markedly from hour to hour during the exposure period. Estimated phase 1 elimination half-lives for *cis* DCP were 3-5 min at 30 to 300 ppm, and 14 min for 900 ppm. Corresponding elimination half-lives for *trans* DCP were about 5 min for lower dose levels, and 27 min for 900 ppm. *Trans* DCP, although not as abundant in the technical as the *cis* isomer, was consistently more abundant in blood during exposure, and was more slowly cleared after cessation of dosing. Blood plateau levels at 30 ppm were 0.085 and 0.12 µg/ml for *cis* and *trans* DCP, respectively. The most profound difference in blood concentrations of isomers at termination of exposure was in 300 ppm rats, where *trans* isomer was over twice the concentration of *cis* isomer. Investigators determined the proportion of absorption in upper and lower respiratory tract (URT and LRT, respectively) after sectioning and catheterizing the tracheae of anesthetized rats. LRT absorption was assessed by analyzing inhaled and exhaled gasses in the isolated caudal portion of the endotracheal tube. URT uptake was estimated by examining input and output gas DCP in a direct unilateral flow model. Sums of LRT and URT uptakes were compared against absorbed dose in similarly anesthetized rats with intact respiratory tracts. These tests evaluated 90 ppm and 150 ppm DCP test atmospheres only. Investigators determined that 73-79% of total absorbed DCP was absorbed in the LRT, the balance of absorbed DCP in the cannulated rats being absorbed in the URT. The sums of these two isolated respiratory tract uptake estimates were acceptably close to measured absorption in the anesthetized intact rat. When expressed as percent of theoretical uptake, LRT and nose-only intact rats absorbed about 50% of available DCP. About 11-16% of dose was absorbed in the URT. Respiratory frequency and tidal volume were assessed with a pressure transducer designed to measure pressure changes in the head-only space. There was a consistent decrease in respiratory rate (breaths/min) with increasing dose, with no consistent change in tidal volume, hence there was a decrease in respiratory minute volume at 300 to 900 ppm. A combination of reduced respiratory minute volume and reduced percent of dose absorbed at the highest dose resulted in a reduction of uptake/(exposure concentration) to less than 50% at 900 ppm compared to 30 ppm rats. Investigators estimated tissue non-protein sulfhydryl (NPSH) content in

homogenates of liver, kidney, or lung immediately after dosing with 0 or 90 ppm DCP (tissue proteins were removed by precipitation with trichloroacetic acid or *m*-phosphoric acid). Liver and kidney NPSH contents were statistically significantly reduced by DCP: 31% reduction of NPSH in kidney and 41% decrease in liver (no NPSH effect in lung). Aldous, Jan. 5, 2015.

50046-0216 282090 Waechter, J. M. and P. E. Kastl, "1,3-Dichloropropene: Pharmacokinetics and metabolism in Fischer 344 rats following repeated oral administration," The Dow Chemical Company, Midland, MI, 12/23/88. Laboratory Study # K-6409-(13). Five rats/sex were dosed daily with 5 mg/kg 1,3-dichloropropene (1,3-D), (54.2% *cis* and 45.8% *trans*), by gavage in corn oil (5 ml/kg) for 14 consecutive days. On day 15, rats were fasted for 8 hrs prior to dosing with 5 mg/kg of *cis/trans*-1,3-dichloropropene, uniformly labeled with ^{14}C, which assayed prior to dosing at 96.3% 1,3-D (53.5% *cis* and 43.0% *trans*). Two additional fasted rats/sex, which had no prior 1,3-D treatment, were treated with the same labeled material. Urine, feces, exhaled CO_2, other expired volatiles, and tissue levels were assessed. Sacrifice was 48 hrs after labeled treatment. Chromatic resolution was not sufficient to routinely separate the *cis* and *trans* isomers of mercapturic acid conjugates, and also not sufficient to separate subsequent sulfoxide and sulfone products from one another. Approximately 62-65% of administered dose was found in urine, 26% in exhaled CO_2, 5% in feces, and 4-6% in tissues and carcass, with no observed sex difference. Disposition in the 2/sex non-pre-treated rats was quite similar. At 48 hrs after dosing of pre-treated rats, highest concentrations of label (about 1 µg equivalent/g tissue) were in bladder and forestomach. Lowest concentrations were in brain and fat (less than 0.1 µg equivalent/g tissue), with about 0.2 to 0.4 µg equivalent/g in other tissues. Urinary excretion of the *cis/trans* N-acetyl cysteine conjugates comprised 26-28% of administered dose. The combined close-eluting sulfoxide and sulfone residues comprised about 14% of administered dose. No other components were characterized. Most excretion occurred within the first 12 hours. There were no clear differences in disposition between sexes or resulting from 14-day pre-treatment vs. naïve rats. This is a valid supplemental study. Aldous, 1/23/15.

50046-058 115135 Stott, W. T., "Implications of the results of a recent human pharmacokinetics study upon interspecies extrapolation of risk," (3-page letter). Stott determined by extrapolation from a human volunteer study [Waechter et al., 1992, Record No. 113124] and from a rat pharmacokinetics study Stott, W. T., and P. E. Kastl, 1986 (published), or DPR unpublished version in Record No. 057488] that humans attain a lower systemic dose than do rats following equivalent inhalation exposure. Stott also concluded [evidently from study by Waechter et al., 1992] that humans rapidly clear Telone from the blood ($T_{1/2}$ probably less than 10 min). Also, humans evidently excrete Telone as conjugates (largely mercapturates, and likely also sulfoxides) to a large degree, perhaps more than do rodents. This letter was not reviewable and thus has no worksheet. Aldous, Jan. 9, 2015.

50046-060 118048 Stott, W. T. and L. L. Calhoun, "Implications of the results of a recent human pharmacokinetics study upon interspecies extrapolation of risk," (3-page letter). This provides a few updates to the above record 50046-058 115135 by Stott (identical titles in both letters), and makes a strong statement that (1) default animal-to-human scaling factors to address metabolic capacity for humans are not appropriate, consideration the data available for human subjects already account for physiological differences, and (2) a default potency calculation

based on the mouse and not the rat already leads to excessively conservative outcomes. This letter was not reviewable and thus has no worksheet. Aldous, Jan. 12, 2015.

50046-0015 932855 Dietz, F. K., E. A. Hermann, and J. C. Ramsey, "The Pharmacokinetics of ^{14}C-1,3-dichloropropene in rats and mice following oral administration," Toxicology Research Laboratory, Dow Chemical U.S.A., Midland, MI. This appears to be an abstract for a professional meeting, with no date given, however this abstract pre-dates the accompanying 9/22/1983 letter in the volume. Investigators reported urinary excretion of an oral dose of Telone was 51-61% of dose in rats, and 63-79% in mice over the 48-hr study period. Feces accounted for 18% and 15% of dose in rats and mice, respectively. Expired CO_2 comprised 6% and 14% of dose in rats and mice. About 2-6% of dose remained in carcasses in either species at 48 hrs. The major identified metabolite was N-acetyl-S-(3-chloroprop-2-enyl) cysteine. A second major metabolite appeared to be a sulfoxide or sulfone of the latter. This abstract was not reviewable and thus has no worksheet. Aldous, Jan. 12, 2015.

50046-0015 932856 Dittenber, D. A, H. D. Kirk, and J. C. Ramsey, "Non-protein sulfhydryl content and macromolecular binding in rats and mice following oral administration of 1,3-dichloropropene," Toxicology Research Laboratory, Dow Chemical U.S.A., Midland, MI. This appears to be an abstract for a professional meeting, with no date given, however this abstract pre-dates the accompanying 9/22/1983 letter in the volume. Investigators administered oral doses of Telone to male F344 rats and to B6C3F1 mice at 0 to 100 mg/kg. After 2 hrs, animals were sacrificed for collection of forestomach, glandular stomach, liver, kidneys, and bladder. Depletion of non- protein sulfhydryl was highest in forestomach (to as low as 17-27% of control levels at 100 mg/kg). Also, tissue binding of label was highest in forestomach and glandular stomach (of tissues sampled). Investigators concluded that these tissues in particular would be particularly sensitive to Telone at high dose levels. This abstract was not reviewable and thus has no worksheet. Aldous, Jan. 12, 2015.

50046-0241 291556 Hotchkiss, J. A., K. M. Mahoney, and F. Zhang, "1-3-Dichloropropene: inhalation, absorption and systemic bioavailability in B6C3F1 mice," The Dow Chemical Company, Midland, MI, 11/16/2015. Laboratory Study # 151067. Male mice were exposed nose-only to technical 1-3-dichloropropene (97.5% purity: 48.1 % *cis* and 49.4% *trans*) at 2.5, 4.8, 10.5, 20, 60, or 150 ppm (11.4, 21.8, 47.7, 90, 271, or 681 mg/m^3) for about 6 hours. Investigators assessed respiratory parameters (breaths/minute, tidal volume, and minute volume). They assayed blood concentrations of the two isomers by GC/MS-MS. Higher doses greatly reduced respiration rate, with 50% reduction at about 17.9 ppm. *Cis* isomer was cleared from blood much more quickly than was *trans*. Blood concentration of cis isomer following exposure was below limits of quantification at 2.5 through 10.5 ppm; then 2, 2, and 157 ng/g, respectively, at 20, 60, and 150 ppm of 1-3-dichloropropene. In contrast, *trans* isomer blood concentrations at 2.5, 4.8, 10.5, 20, 60, and 150 ppm 1-3-dichloropropene were 2, 2, 7, 19, 16, and 674 ng/g, respectively. Thus the highest dose exceeded clearance mechanisms, and low dose blood levels were not linearly related to exposure. Results in mice qualitatively resemble those of rat and human studies, with *cis* isomer consistently more rapidly cleared than *trans*. Aldous, 6/29/16.

GUIDELINE ACUTE STUDIES ON ACTIVE INGREDIENT

Acute oral toxicity, rat ** (related non-guideline studies included)

50046-032; 62068; Telone II Soil Fumigant: Acute Oral Toxicity Study In Fischer 344 Rats; Mammalian and Environmental Toxicology Research Laboratory, Health and Environmental Sciences, Dow Chemical Co., Midland MI, Project ID HET M-003993-017A, 2/9/87; (Telone II Soil Fumigant); Dose levels 100, 500, and 1000 mg/kg of a 10% (v/v) solution of the test material in corn oil; 5 animals/sex/dose; Clinical Observations-lethargy, diarrhea, lacrimation, palpebral closure, labored respiration, facial soiling and/or rough hair coat in some animals of all dose groups; LD50 (M) = 300 mg/kg, LD50 (F) = 224 mg/kg; CAT II; Acceptable; JSB, 5/2/88

50046-0223 283294 Toyoshima, S., R. Sato, and S. Sato, "The acute toxicity test of Telone* II in mice," Japan Experimental Medical Research Institute Co., LTD, 6/30/78. This is a brief report of an old study, using 92% purity Telone II in JCL:ICR mice. Reported LD_{50} by gavage (corn oil vehicle) was 640 mg/kg in males and also 640 mg/kg in females. Reported LD_{50} by subcutaneous treatment (corn oil vehicle) was 330 mg/kg in males and also 345 mg/kg in females. "Percutaneous" exposure (fixed application of 1 ml/kg over 3 x 2 cm^2 of skin) caused no deaths and did not elicit any findings of toxicity, hence LD_{50} > 1.211 mg/kg in both sexes. Not acceptable and not upgradeable, as test article was unlikely to represent modern technical Telone II, and report lacked sufficient detail to be suitable for a worksheet. Aldous, 3/30/15.

50046-0223 283295 Toyoshima, S., R. Sato, and S. Sato, "The acute toxicity test of Telone* II in rats," Japan Experimental Medical Research Institute Co., LTD, 6/30/78. This is a brief report of an old study, using 92% purity Telone II in Wistar rats. Reported LD_{50} by gavage (corn oil vehicle) was 560 mg/kg in males and also 510 mg/kg in females. Reported LD_{50} by subcutaneous treatment (corn oil vehicle) was 400 mg/kg in males and also 366 mg/kg in females. "Percutaneous" exposure (fixed application of 1 ml/kg over 4 x 5 cm^2 of skin) caused no deaths and did not elicit any findings of toxicity, hence LD_{50} > 1.211 mg/kg in both sexes. Not acceptable and not upgradeable, as test article was unlikely to represent modern technical Telone II, and report lacked sufficient detail to be suitable for a worksheet. Aldous, 3/30/15.

Acute dermal toxicity (see note at end of 1-liner)

50046-032; 62069; Telone II Soil Fumigant: Acute Dermal Toxicity Study In New Zealand White Rabbits; Mammalian and Environmental Toxicology Research Laboratory, Health and Environmental Sciences, Dow Chemical Co., Midland MI, Project ID HET M-003993-017D, 3/18/87; (Telone II Soil Fumigant); Dose levels 200 and 1000 mg/kg; 5 animals/sex/dose; 24 hour exposure period, occluded patch; Clinical Observations-restless, squealing, lethargic, diarrhea, anorexia, labored breathing; Dermal Irritation- all animals had skin and/or subcutaneous tissue irritation at the dermal site, subcutaneous, necrosis, erythema, edema, and/or crusts; Report states the LD50 (M/F) = 333 mg/kg which falls into a CAT II. Unacceptable, as guidelines require at least three dose levels to produce test groups with a range of toxic effects and mortality rates; J. Berliner, 5/3/88. NOTE: Current evaluation guidelines would have allowed acceptance of this study, since dose levels identified a toxicity category (Aldous, 6/25/15).

Acute inhalation toxicity, rat **

**50046-032; 62070 "Telone II Soil Fumigant: An Acute Vapor Inhalation Study In Fischer 344 Rats," Mammalian and Environmental Toxicology Research Laboratory, Health and Environmental Sciences, Dow Chemical Co., Midland MI, Project ID HET M-003993-018, 4/30/87. Telone II Soil Fumigant, Lot # TB-860825-5, was administered at nominal/analytical 1076/1035, 946/855, 820/775 ppm to 5 animals/sex/dose for a 4 hour exposure period. Clinical observations were tremors, convulsions, salivation, lacrimation, diarrhea, lethargy, and other signs of altered central nervous system function. LC50 (M) was between 1035 and 855 ppm, LC50 (F)= 904 ppm. Conversion from ppm to mg/l: LC50 (M) between 4.688 mg/l and 3.873 mg/l,LC50 (F)= 4.095 mg/l. Necropsy: clear facial soiling and/or hemorrhages in multiple lung lobes. Category III; Acceptable; J. Berliner, 5/3/88.

50046-0221 282875 Cracknell, S., G. Jackson, and C. Hardy, "Telone* II (1,3-dichloropropene) acute inhalation study in rats, 4 hour exposure," Huntingdon Research Centre, Ltd., 3/25/87. Report designation: DWC/484. Five Wistar-derived rats/sex/group were dosed for 4 hours with Telone II (Lot 071.3054/062), 98.4% purity, by whole-body inhalation at 0, 1.62, 2.64, 2.70, or 3.07 mg/L (assayed mean concentrations). Rats were observed at 6 intervals during exposure, and daily during a 14-day post-dose observation period. All rats survived except for 3/5 males and 3/5 females at 3.07 mg/L. All male groups showed a body weight loss at day 1 weighing, followed by normal subsequent gains in survivors. Body weights were unaffected in 1.62 mg/L females, but other female groups suffered body weight losses on day 1, followed by normal weight gain patterns thereafter. An exception was that the surviving 3.07 mg/L females appeared to require an additional 5 days for weight gains to normalize. Common signs at the lowest dose (1.62 mg/L) during exposure were partial closing of eyes, slow respiratory rate, and irregular respiratory movements during exposure in all rats; and hunched posture, restlessness, exaggerated respiratory movements, and pawing behavior in some rats. Clinical signs for 1.62 mg/L were normal by the day after treatment, whereas symptoms continued for up to 5 days at 3.07 mg/L. LC_{50} was thus between 2.70 and 3.07 mg/L in both sexes. Study is not acceptable, but upgradeable on submission of a standard curve and sample calculation to validate the reported assayed test atmosphere content. Aldous, April 6, 2015.

50046-0217 282091 Nitschke, K. D., J. W. Crissman, and D. J. Schuetz, "*cis*-1,3-Dichloropropene: acute inhalation study with Fischer 344 rats," The Dow Chemical Company, Midland, MI, 9/27/90. Laboratory Study # K-020256-005. Groups of 5 rats/sex were dosed by whole-body inhalation for 4 hours with time-weighted average concentrations of 573, 771, or 1020 ppm of cis-1,3-dichloropropene. Test article was 95.6% cis-1,3-dichloropropene, with minor amounts of two assayed components: 1.5% trans-1,3-dichloropropene, and 0.2% 1,2-dichloropropane. All rats died at 1020 ppm during or shortly after exposure. All males died at 771 ppm, two of which did not survive more than 30 minutes after the end of dosing. Also 3/5 females died at 771 ppm. All rats survived at 573 ppm. Clinical signs of labored breathing and "eyelids closed" were each observed in 1/sex at 573 ppm on the day of exposure, with no clinical signs in 573 ppm rats after the day of treatment. At 573 ppm, body weights were remarkably diminished on weighing days 2 and 4, with substantial body weight recovery evident by day 8. Gross examinations revealed unilateral opacity in two high dose males, visceral congestion in four of five 771 ppm males, liver and lung congestion in all high dose males, hydrothorax in two 771 ppm males, corneal opacities in the majority of 1020 ppm females, liver and lung congestion

in all high dose females, and lung edema in one mid-dose female. All 573 ppm rats were grossly normal at termination. Nominal LC_{50} was estimated to be 670 ppm and 744 ppm for males and females, respectively. For males, the most sensitive gender, mass/volume units of LC_{50} are 3.04 mg/L. This is a supplementary study on a test article enriched in the *cis* isomer. Aldous, 2/2/15.

50046-0206 273926 "Acute inhalation reference concentration assessment for 1,3-dichloropropene," 07/18/2013. This is a discussion on acute inhalation reference concentration assessment by Maier, A., L. Haber, and A. Parker. A DPR review of this submission by L. M. Hall is included in this volume.

50046-0223 283297 Stevenson, D. E., "Toxicity of soil fumigants: acute inhalation toxicity of 1,3-dichloropropene," Shell Toxicology Laboratory (Tunstall), March, 1977. [Technical was 51% cis and 43.4% trans 1,3-dichloropropene, with 1% epichlorohydrin.] Male and female Wistar rats were dosed by whole-body inhalation for 4 hours to establish an LC_{50}. Calculated LC_{50} was 729 ppm for both sexes. This very brief (3-page) summary report on an outdated technical formulation is not suitable for a DPR worksheet. Aldous, 3/30/15.

50046-0223 283298 Yakel, H. O., and R. J. Kociba, "Acute inhalation toxicity of M-3993 (Telone II) in rats," The Dow Chemical Co., Midland, MI, 6/17/77. Test article was "M-3993," composed of 92% 1,3-dichloropropene and 8% inerts (not further described). Ten Spartan Sprague-Dawley rats/sex were dosed for 1 hour at 5.2 mg/L (nominal concentration), with reported mean diameter of 2.96 microns (99% of particles < 6 micron diameter). "Slight transitory eye irritation" (not further described) was observed during exposure. No behavioral changes were noted, and autopsy findings after 2 weeks were normal. This brief summary report, not a standard design, too brief for thorough review, and likely on an outdated technical formulation, is not suitable for a DPR worksheet. Aldous, 3/20/15.

50046-0223 283296 Landry, T. D., and S. M. Krieger, "Telone II soil fumigant: 1-hour acute nose-only inhalation toxicity study in Fischer 344 rats," The Dow Chemical Co., Midland, MI, Jan. 6, 2003. Five male rats were dosed once as indicated at 14000 ppm Telone II [97.5% a.i., (cis and trans)]. All rats survived the 1-hr exposure, but one died within an hour after treatment, and all were dead by the next day. Major clinical signs included decreased muscle tone, decreased resistance to removal, decreased extensor thrust, decreased reactivity to stimuli, inability to walk, eyelids partially closed, cold to touch, slow and labored respiration, and soiled fur (mostly urine). Mottled lungs and serosanguineous muzzle soiling were the most common gross pathology findings. This was a valid supplementary study, but not of standard design and featuring only one very high dose, hence no DPR worksheet is appropriate. Aldous, 3/20/15.

Primary eye irritation, rabbit **

50046-032; 62071; Telone II Soil Fumigant: Primary Eye Irritation Study In New Zealand White Rabbits; Mammalian and Environmental Toxicology Research Laboratory, Health and Environmental Sciences, Dow Chemical Co., Midland MI, Project No. HET M-003993-017C, 1/13/87; (Telone II Soil Fumigant); Dose level 0.1 ml; 4M and 2F rabbits with unwashed eyes; left eye remained untreated and served as a control; 7 Day Readings (Unwashed) positive effects only: 1/6 animals score of 2 for redness, and 1/6 animals score of 1 for corneal opacity
14 Day Readings (Unwashed): 6/6 animals score of 0 for redness, chemosis, discharge, and corneal opacity; CAT II; Acceptable; JSB, 5/3/88

Primary dermal irritation **

50046-032; 62072; Telone II Soil Fumigant: Primary Dermal Irritation Study In New Zealand White Rabbits; Mammalian and Environmental Toxicology Research Laboratory, Health and Environmental Sciences, Dow Chemical Co., Midland MI, Project ID HET M-003993-017B, 1/7/87; (Telone II Soil Fumigant); Dose level 0.5 ml; 4 hour exposure period, occluded patch; 6 animals used; 72 Hour Readings (Intact): Erythema- 5/6 animals score of 2, 1/6 animals score of 1. Edema- 2/6 animals score of 2, 2/6 animals score of 1, and 2/6 animals score of 0; CAT III; Acceptable; JSB, 5/3/88

Dermal sensitization ** †

****50046-0032 062073** Jeffrey, M. M., "Telone II Soil Fumigant: Dermal sensitization potential in the Hartley albino guinea pig," The Dow Chemical Company, Midland, MI. March 12, 1987. Laboratory Study # HET M-003993-017E. Ten Hartley albino guinea pigs/group were dosed with either 0.4 ml 0.1% Telone II in mineral oil, a positive control of 10% DER 331 in DOWANAL DPM (eventually reduced to 5% solution due to erythema during the induction phase), or mineral oil vehicle. The above treatments were undertaken weekly three times to the clipped dorsal skin, secured under dressing for 6 hour periods each time, for the induction phase. Two weeks after the last induction phase, a comparable challenge dose was administered. Treatment sites were examined on the day after dosing for each induction treatment, and 24 and 48 hours after the challenge dose. Induction treatments of Telone II did not cause irritation after the first or second treatment. Four of 10 Telone II animals showed slight erythema after the third and final induction. At 48 hours after challenge, 8/10 Telone II animals displayed slight erythema, and 1/10 Telone II animals displayed moderate erythema. The overall response of Telone II animals at challenge treatment was thus 9/10. Five of 10 positive controls responded with slight erythema by 24 hours at challenge. Mineral oil animals were uniformly negative for both induction and challenge phases. Telone II is a **sensitizer**. This study is acceptable. Aldous, 1/30/15.

Acute Studies with known outdated technical material

50046-0011 932843 "Acute Toxicological Properties of Experimental Nematicide Formulation M-3993 Containing 1, 3 Dichloropropene," Dow Chemical, Midland, MI, 09/01/1975. This is a report of several acute studies of an old active ingredient containing 1% epichlorohydrin. Data are unlikely to be useful any more. Acute NOEL (rat) was calculated to be 713 mg/kg (M) and 470 mg/kg (F). Eye irritation (rabbits) indicated slight to moderate corneal effects at 24 hrs, with clearing by day 8. Skin irritation methodology (rabbits) was unlike modern studies, and did not follow animals for the requisite time after dosing: some edema was evident at 24 hours. Acute percutaneous absorption in rabbits indicated a "mixed rabbit sexes" NOEL of 504 mg/kg. No DPR worksheet is relevant. Aldous, Feb. 2, 2015.

SUBCHRONIC STUDIES (may include subacute probe studies)

Oral subchronic toxicity, rodent: **

**50046-073 126523 Haut, K. T., K. A. Johnson, S. N. Shabrang, and W. T. Stott, "Telone II soil fumigant: 13-week dietary toxicity and 4-week recovery studies in Fischer 344 rats", The Dow Chemical Co., Midland, 1/8/93. Laboratory Project Study ID: M-003993-028. Fischer 344 rats, 20/sex/group, were dosed with 0, 5, 15, 50, or 100 mg/kg/day 1,3-dichloropropene in diet

(test article was microencapsulated in spheres composed of an 80%/20% starch/sucrose matrix). All rats were exposed for 13 weeks, at which time 10/sex/group were sacrificed, whereas the remaining 10/sex/group were maintained off treatment for 4 weeks to evaluate recovery. The NOEL for toxic endpoints is 5 mg/kg/day (dose-related non-glandular stomach basal cell hyperplasia at 15 mg/kg/day and above). Small but statistically significant decrements in body weight at 5 to 15 mg/kg/day in males and 15 mg/kg/day in females were plausibly treatment-related, but of unlikely toxicological significance (small degree of change or nearly flat dose-response curve). **No adverse effects. Acceptable**. Aldous, 9/21/99.

50046-059; 117681; "Telone II Soil Fumigant: Palatability and Two-Week Dietary Probe Studies in Fischer 344 Rats," K.T. Haut *et al*. Non-guideline; Rat; The Toxicology Research Laboratory, Health and Environmental Sciences, The Dow Chemical Company, Midland, MI; Study No. M-003993-026; 8/3/92. Telone II Microencapsulated (a.i.: 42.7%); five rats/sex per group received 0, 10, 25, 50, 100 mg/kg/day (based on a.i. concentration? in starch/sucrose suspension) for 14 days, dietary; No mortality; Reduced body weight gain and food consumption (50 and 100 mg/kg/day); No treatment-related effect on hematology or ophthalmology; Necropsy: no treatment-related lesions; Histopathology: hyperkeratosis in the nonglandular mucosa of the stomach, and thickened nonglandular mucosa of the stomach (considered to be localized irritant effect): (both findings at 50 and 100 mg/kg/day, also 1/5 males had thickened non-glandular mucosa at 25 ppm). NOEL cannot be established until analytical data on the dietary preparations are submitted, but provisionally is 10 mg/kg/day for males and 25 mg/kg/day for females. Study is supplemental. (Moore, 7/14/94)

50046-074 126524 Haut, K. T., K. E. Stebbins, S. N. Shabrang, and W. T. Stott, "Telone II soil fumigant: 13-week dietary toxicity study in B6C3F1 mice", The Dow Chemical Co., Midland, 1/8/93. Laboratory Project Study ID: M-003993-029. Mice, 10/sex/group, were dosed with 0, 15, 50, 100, or 175 mg/kg/day 1,3-dichloropropene in diet (test article was microencapsulated in spheres composed of an 80%/20% starch/sucrose matrix). Mice were exposed for 13 weeks in a standard subchronic study design. Decreased size of hepatocytes was observed in all male treatment groups ("very slight" degree in all cases): this was attributed by the authors to a decrease in glycogen content. No comparable findings were reported in females. A NOEL for body weight decrements was 15 mg/kg/day for both sexes. Decreased circulating triglyceride levels were found in 100 to 175 mg/kg/day females. All findings were consistent with reduced nutritional status, thus no target organ toxicity was evident. **Acceptable, with no adverse effects. Aldous, 9/20/99.

Inhalation subchronic toxicity, rodent: † (two valid supplementary studies)

50046-038 071713 Stott, W. T., J. T. Young, and L. L. Calhoun, "Telone II Soil Fumigant: A 13-Week Inhalation Study in Rats and Mice." (Dow, 11/30/84) Telone II, 90.9%, lot WP-82-1111-56, was given by whole-body inhalation for 6 hours/day, 5 days/week for 13-weeks to 10 Fischer 344 rats per sex and to 10 B6C3F1 mice per sex, at 0, 10, 30, 90 or 150 ppm nominal chamber concentration. Body weights were significantly lower at 90 and 150 ppm in rats, dose-related, from treatment day 3 onward. Mouse body weight decrements were consistently reduced at 150 ppm, and occasionally at 90 ppm. Food consumption was not assessed in either species. The only histopathology findings in **rats** were degeneration in the olfactory epithelium at 150 ppm, and hyperplasia of the respiratory epithelium in both sexes, with severity increased

from 90 to 150 ppm. Rat NOEL = 10 ppm based on hyperplasia of the respiratory epithelium in 2/10 males at 30 ppm. **Mice** had degeneration in the olfactory epithelium and hyperplasia of the respiratory epithelium in all observed survivors of both sexes at 90 to 150 ppm, with a clear dose-response for severity in that range. Slight olfactory respiratory metaplasia was also observed in all 150 ppm males and in most 150 ppm females (described as replacement of sensory epithelia with ciliated cells typical of epithelia of non-sensory regions of the respiratory tract). In addition, most female mice also displayed epithelial cell hyperplasia of urinary bladder transitional cells, such that affected areas had remarkably increased cell layers of epithelial cells. Rat NOEL = 10 ppm based on hyperplasia of the respiratory epithelium in 2/10 males at 30 ppm. Mouse NOEL = 30 ppm. Report contains valid supplementary data (Gee, 5/22/89, re-examined for a targeted review by Aldous at request of Risk Assessment staff on 1/21/15).

50046-010 036551 Coate, W. B., "90-Day Inhalation toxicity Study in Rats and Mice: Telone® II." The original Hazleton report was completed on 5/15/79. A key addendum consisting of re-evaluation of nasal cavity histopathology was undertaken for all groups of both species (July 9, 1979). This was not a guideline study, but was intended as range-finder for future studies. Ten rats/sex and 10 mice/sex were exposed by whole-body inhalation to Telone II, "Production Grade," purity unspecified, at 0, 10, 30, or 90 ppm for 6 hours/day, 5 days/week, for 13 weeks (65 exposures). NOEL for female rats is 12 ppm, based on decreased cytoplasmic content and disorganization of cell nuclei in nasal epithelial cells of the nasal septum and dorsal turbinates. NOEL for male rats is 32 ppm, based on the above histopathology in all 93 ppm rats. There were body weight gain decrements in both sexes at 93 ppm, and some individuals of both sexes of rats at that dose had individual cell necrosis in nasal epithelia. NOEL for mice is 32 ppm, based on body weight gain decrements in both sexes, and on decreased cytoplasmic content in nasal epithelial cells of the nasal septum and dorsal turbinates in females. This is a valid supplementary study, with nasal turbinate histopathology designated as a "possible adverse effect." (F. Martz, 4/29/86. This report was later reviewed to support risk assessments on 7/6/89 by C. Lewis, and on 1/29/15 by C. Aldous).

50046-0013 932848 Parker, C. M., W. B. Coate, and R. W. Voelker, "Subchronic inhalation toxicity of 1,3-dichloropropene/1,2-dichloropropane (D-D) in rats and mice," Journal of Toxicology and Environmental Health 9:899-910 (1982). Test article was an old Shell product comprised principally of *cis*-1,3-D (25%), *trans*-1,3-D (27%), and 1,2-dichloropropane (29%). Investigators reported significantly increased incidence of slight "diffuse hepatocytic enlargement" in male mice, and a marginal increase in female mice, with no notable findings of any kind in rats. Given the difference between this and any contemporary products, this study has no apparent importance. Aldous, Feb. 1, 2015. No worksheet.

Oral subchronic toxicity, non-rodent:

046 075537 "Telone II: 13-Week Dietary Toxicity Study in Beagle Dogs." Quast, J. F., Dow Chemical Company, August 1, 1989. The 3-page letter was submitted as an adverse effects disclosure for microcytic hypochromic anemia in the 13-week study in beagle dogs. Doses were 0, 130, 380 or 1000 ppm with Telone II incorporated in a starch sucrose matrix and administered in the dog chow. The letter contains no data but states the anemia was dose-related. Page 2 of the letter indicates "minimal effect in one dog of each sex" at 130 ppm, presumably for microcytic hypochromic anemia. Some dogs were being maintained after dosing for further

study. The final report has not yet been received by CDFA. (Gee, 4/27/90). NOTE: As of 2/2/15, no finished dog subchronic dietary report has been received (C. Aldous).

50046-043 protocol (dated 4/12/89) for the 13-week dietary dog study (see Record No. 075537, above). (Gee, 5/23/89).

Dermal toxicity, 21/28-day or 90-day:

No study submitted.

CHRONIC STUDIES

Combined (chronic and oncogenicity), rat:

Oral route ** †

****50046-098 140562** Stott, W. T., K. A. Johnson, T. K. Jeffries, K. T. Haut, and S. N. Shabrang, "Telone*II Soil Fumigant: Two-year chronic toxicity/oncogenicity study in Fischer 344 rats". The Toxicology Research Laboratory, The Dow Chemical Co., Midland MI, 8/15/95. Laboratory Project Study ID: M-003993-031. Microencapsulated Telone*II, purity 95.8% 1,3-dichloropropene (50.7% cis/45.1% trans), was admixed with the diet at 0, 2.5, 12.5 or 25 mg/kg/day and fed to 50 F344 rats/sex/group for 24 months. Additional rats (10/sex/group) were allocated for a 1-yr interim sacrifice. No definitive NOEL is present in this study: hepatocellular eosinophilic foci appear increased in number and/or degree at all dose levels. Characteristic findings at 12.5 to 25 mg/kg/day include forestomach basal cell hyperplasia, reduced body weight, and reduced food consumption. Hepatocellular tumors (primarily adenomas) were significantly elevated in high dose males, and non-significantly elevated in mid-dose males and high dose females. The 1996 DPR review noted an apparent elevation in uterine endometrial stromal polyps in 25 mg/kg/day females, however supplemental data in Document No. 50046-104, Record No. 151747 present historical control data which do not support a treatment effect. A number of other changes (particularly reductions in degree or incidence of normal aging lesions) indicate altered physiology or nutritional status influencing the progress of normal geriatric changes in high dose rats. Study is **acceptable**. Liver tumors are "possible adverse effects". Kishiyama and Aldous, 4/19/96; Aldous, 3/11/97.

50046-072 126522 This 116-page report is the 1-yr interim report of Record # 140562 above. There is no essential new information in this report , hence no worksheet. Aldous, 7/15/99.

F**ollowing is a mechanistic study, primarily applicable to study 50046-098 140562, above.**
Klaunig, J. E., S. C. Gehen, Z. Wang, P. J. Klein, R. Billington, "Mechanism of 1,3-dichloropropene induced rat liver carcinogenesis," ToxSci Advance Access published 10/28/14. Participants were affiliated with Indiana University and Dow Agro Sciences. All test animals were F344 rats, which were pre-treated with dimethylnitrosamine (DEN) twice (at 6 and at 7 weeks of age, 100 mg/kg each time) to initiate pre-neoplastic foci in the liver. Sixteen weeks later, groups of 11 were dosed as follows: (1) 1,3-Dichloropropene (1,3-D): 52.5% *cis*- and 46.7% *trans*-, without stabilizers such as epichlorohydrin; groups of 11 were administered by gavage in corn oil daily for 30 days, for 60 days, or for 30 days followed by 30 days of recovery; (2) phenobarbital (PB), 80 mg/kg/day by gavage in saline; groups were dosed daily for 30 days,

for 60 days, or for 30 days followed by 30 days of recovery; or (3) negative controls were treated with corn oil for 30 days or for 60 days. Liver tissues were fixed, embedded, and stained with H&E. Focal liver lesions were also assessed with immunohistochemical techniques targeting placental glutathione S-transferase (GSTP), which is used as a marker for pre-neoplastic lesions, and which is often associated with phenobarbital enhancement of liver tumors. Also, BrdU immunohistochemical techniques (after osmotic pump infusion for 7 days prior to sacrifice) were used to assess cell replication. Investigators also employed a 2-dimensional morphometric analysis to evaluate sizes of focal lesions. Body weights did not vary systematically with treatments. Liver weights were greatly increased in PB groups after 30 days and 60 days, with no significant differences after 30-day recovery. 1,3-D had no influence on liver absolute or relative weights. BrdU labeling index was elevated about 2-fold in GSTP-negative foci at 30 and at 60 days in 1,3-D rats, and at 60 days in PB rats. There were no such changes in GSTP-positive foci. Total numbers of GSTP-positive foci were unchanged with 1,3-D. In contrast, PB elicited an increase in GSTP-positive foci correlated with exposure duration between 30 and 60-day exposures, with a significant residual elevation of GSTP-positive foci in PB rats after the recovery phase. GSTP-negative foci were statistically significantly increased in number following 1,3-D treatment for 30 or 60 days, with a modest elevation remaining after recovery. PB did not have a consistent effect on GSTP-negative foci. Volume of GSTP-positive foci (assessed by 2-dimensional analyses) was quite variable, and the only statistically significant finding was an increased total volume of foci in the 60-day PB group. Volumes of GSTP-negative foci were increased in 1,3-D groups at 30 and 60 days. There was also a comparable increase in volume of GSTP-negative foci in PB rats at 60 days. An assessment of numbers and size class of GSTP-positive foci found a progressive increase in size and number of the PB groups compared to the other two groups from the 30-day to 60-day exposure intervals. A small but visually evident increase in focal size class was evident in the recovery PB rats. An assessment of numbers and size class of GSTP-negative foci found 1,3-D foci to have increased abundance among small to medium-sized foci after 30 and at 60 days exposure, with no residual 1,3-D effect after the recovery phase. PB rats treated for 60 days had slightly elevated numbers of relatively large GSTP-negative foci compared to other groups. This report provides useful data, showing that 1,3-D is capable of promoting previously-induced GSTP-negative foci with an enhancement of DNA synthesis, without eliciting the GSTP-positive foci that are characteristic of PB exposure, and which are also associated with non-genotoxic tumor promotion. Examined tissues in this study returned to normal appearance and function upon removal of 1,3-D exposure. Aldous, 2/2/15.

50046-010 036552 "Toxicology and Carcinogenesis Studies of Telone II in F344/N Rats and B6C3F1 Mice." (NTP Technical Report Series No. 269, Frederick Cancer Research Center, 5/85). **This 1-liner summarizes results in rats**. Telone II (1,3-dichloropropene, 87.5% pure, with epichlorohydrin as stabilizer) was administered to 52/sex/group at 0, 25, or 50 mg/kg by oral gavage "3 times a week" for the lifetime study. An additional 25/sex/group constituted satellite groups for general toxicity evaluation, with sacrifices at 9, 16, 21, 24 and 27 months of 5/sex/group. Study is scientifically valid but unacceptable and not upgradeable because it was not designed to address FIFRA guidelines. **Forestomach** was a target organ, with primary non-neoplastic lesion of basal cell hyperplasia incidence (out of 52) in control through high dose males of 1, 3, and 9, and in females of 0, 0, and 12. Respective forestomach squamous cell papilloma incidences in the lifetime study were 1, 1, and 9 for males, and 0, 2, and 3 for females.

Respective forestomach squamous cell carcinoma incidences were 0, 0, and 4 in males, with no squamous cell carcinomas in females. **Liver** did not show non-neoplastic change with dose, but tumor incidence appeared to be meaningfully elevated in males. Incidence of "neoplastic nodule" in control through high dose lifetime study males was 1, 6, and 7; and for corresponding females was 6, 6, and 10. Incidence of hepatocellular carcinoma was 0, 0, and 1 in respective males, with no carcinomas in females. Forestomach pathology, including tumors, is a "possible adverse effect." Study was initially reviewed on 1/16/86 by Martz. Aldous made edits without a new worksheet on 2/3/15.

50046-0240 291161 Kelly, C. M., "A chronic toxicity and oncogenicity study with DD-92 in the rat via oral gavage administration," Huntingdon Life Sciences, East Millstone, NJ, 1/21/98. Laboratory Study # 95-2379. This was designated by Dow as a "Non-GLP Study." This is a 50-page report containing only one page of tabular data, without any individual data. CD rats, 75/sex/group, were dosed daily by gavage with 0, 2, 10, or 25 mg/kg/day 1-3-dichloropropene (98.4% purity) in corn oil vehicle (5 ml/kg b.w.) for 23 months (male) or 24 months (female). Ten/sex of each group were designated for 1-yr interim sacrifice. Body weights of 25 mg/kg/day males were reduced through week 72. There were subtle increases in incidence or degree of forestomach squamous cell hyperplasia and/or hyperkeratosis at 10 to 25 mg/kg/day, suggestive of a dose-response, with an apparent NOEL of 2 mg/kg/day. No oncogenicity was reported. Report is designated as supplementary data. Aldous, July 31, 2016.

Inhalation route †

****50046-0031 060677** Lomax, L. G., L. L. Calhoun, W. T. Stott, and L. E. Frauson, "Telone* II soil fumigant: 2-year inhalation chronic toxicity-oncogenicity study in rats," The Dow Chemical Company, Midland, MI, 7/13/87. Laboratory Study # M-003993-009R. Test article was 1,3-Dichloropropene, 92.1% (cis 49.5% and trans, 42.6%) stabilized with soybean oil. For the lifetime study, 50 F344 rats/sex/group were exposed by inhalation 6 hours/day, 5 days/week for 2 years - whole body exposure - at 0, 5, 20 or 60 ppm nominal. Histopathology of interest was mainly limited to nasal olfactory epithelium (decreased thickness, mainly bilateral; and erosions, most commonly bilateral). In some cases, the submucosa underlying the olfactory epithelium showed slight to moderate fibrosis. There were no treatment-related tumors in any tissue. Except for one 20 ppm male, the nasal histopathology was limited to 60 ppm rats, with incidences highest in males. Thus NOEL for males = 5 ppm (due to the one individual with nasal pathology similar to common responses in 60 ppm rats). NOEL for females = 20 ppm. Body weights were modestly but statistically significantly reduced in 60 ppm males and females for the approximately the first year of the study. ACCEPTABLE with possible adverse chronic effects (above nasal olfactory epithelial responses). (Gee, 7/11/88, re-evaluation by Aldous on 1/26/15 at the request of Risk Assessment Group).

50046- 005 036218 Stott, W. T., L. G. Lomax, L. L. Calhoun, and J. F. Quast, , "Telone* II soil fumigant: 2-year inhalation chronic toxicity-oncogenicity study in rats – **interim report: 6- and 12-month interim sacrifice of rats**," The Dow Chemical Company, Midland, MI, 9/27/85. This was the satellite study to the rat combined study (DPR Document No. 50046-0031, Record No. 060677, above). Rats were dosed in the same chambers concurrently with that lifetime study, with groups of 10/sex/group designated for 6- and 12-month sacrifices. At respective terminations, rats were evaluated for hematology, clinical chemistry, urinalysis, and histopathology. Except for modest but consistent body weight decrements in both sexes at 60

ppm, this study was uneventful. Histopathology examination included nasal tissues, and was uniformly negative. This satellite study was initially examined by Martz on 11/13/86, and was re-evaluated without an additional worksheet by Aldous on 1/15/15.

Chronic, dog ** †

****50046-061 117410** Stott, W.T., Stebbins, K. E., Haut, K. T., Quast, J. F., and Shabrang, S. N.; "Telone*II soil fumigant: One-year dietary toxicity study in beagle dogs", The Dow Chemical Co., Midland, Study ID M-003993-024, 7/22/92. Dogs were fed diets containing microencapsulated Telone*II at 0, 0.5, 2.5, or 15 mg/kg/day for 1 year. NOEL = 2.5 mg/kg/day [hematology profile typical of hypochromic, microcytic anemia: related to increased hematopoiesis in bone marrow and extramedullary hematopoiesis in spleen in both sexes]. Clinical signs in 2 high dose males of pale skin/mucous membranes apparently reflected the anemia. Body weights were depressed and relative liver weights were increased in both sexes at 15 mg/kg/day. The relatively low NOEL for signs of anemia constitutes a "**possible adverse effect**". **Acceptable**; Aldous, 11/15/93.

Oncogenicity, mouse ** † (adverse effects in inhalation guideline study only)

****50046-0029 060675** Stott, W. T., K. A. Johnson, L. L. Calhoun, S. K. Weiss, and L. E. Frauson, "Telone* II Soil Fumigant: 2-year inhalation chronic toxicity-oncogenicity study in mice," The Dow Chemical Company, Midland, MI, 7/13/87, Laboratory Study # M-003993-009. In the main oncogenicity study, fifty B6C3F1 mice/sex/group were dosed by whole-body inhalation for 6 hours/day, 5 days/week for a total of 510 exposure days in an oncogenicity study. [See DPR Record No. 036219 in Document No. 50046-0006 for the associated chronic study component (with 6-month and 1-yr sacrifices)]. Test article was 1,3-Dichloropropene, 92.1% (cis 49.5% and trans, 42.6%) plus 1,2-dichloropropane 0.7%, 1,3-dichloropropane 1.8%, 1-chlorohexane 1.1% and the remainder a mixture of isomers of chlorohexane, chlorohexene and dichloropropene, Lot TB831213-4. Nominal doses were 0, 5, 20, or 60 ppm (not corrected for purity). Exposure corresponds to 0, 22.7, 90.8, or 272.4 mg/m^3 nominal, uncorrected for purity of 92%, so content of the active ingredient was correspondingly lower (i.e., 20.9, 83.6, or 251 mg/m^3) adjusted for purity. NOEL = 5 ppm, based on urinary bladder mucosal hyperplasia in both sexes, and on hyperplasia and hypertrophy of the nasal respiratory epithelium (bilateral) in females. The nasal respiratory epithelium response was nearly universal in both sexes at 60 ppm. In addition, there were aggregations of lymphoid cells in the urinary bladder submucosa in 60 ppm females, hyperplasia of the non-glandular mucosa of the stomach in 60 ppm males, and degeneration of the olfactory epithelium of nasal passages in both sexes at 60 ppm. There was a statistically significant increase in incidence of the common tumor, bronchioalveolar adenoma, in 60 ppm males. This study is **acceptable**, with possible **adverse effects** (bronchioalveolar adenoma, major reactions in nasal respiratory and olfactory epithelia, and urinary bladder mucosal hyperplasia (J. Gee, 7/12/88). The study was re-examined by Aldous in conjunction with a risk assessment (1/14/15).

50046-0006 036219 Yano, B. L., L. L. Calhoun, W. T. Stott, K. A. Johnson, S. K. Weiss, and D. J. Schuetz, "Telone* II Soil Fumigant: 2-year inhalation chronic toxicity-oncogenicity study in mice – Interim report: 6- and 12-month exposures," The Dow Chemical Company, Midland, MI, 9/27/85 (for chronic phase), Laboratory Study # M-003993-009. In this chronic phase associated with an oncogenicity study (see DPR Record No. 060675), ten B6C3F1 mice/sex/group were dosed by whole-body inhalation for 6 hours/day, 5 days/week for either 6

or 12 months. Test article was 1,3-Dichloropropene, 92.1% (cis 49.5% and trans, 42.6%) plus 1,2-dichloropropane 0.7%, 1,3-dichloropropane 1.8%, 1-chlorohexane 1.1% and the remainder a mixture of isomers of chlorohexane, chlorohexene and dichloropropene, Lot TB831213-4. Nominal doses were 0, 5, 20, or 60 ppm (not corrected for purity). Exposure corresponds to 0, 22.7, 90.8, or 272.4 mg/m^3 nominal, uncorrected for purity of 92%, so content of the active ingredient was correspondingly lower (i.e., 20.9, 83.6, or 251 mg/m^3) adjusted for purity. NOEL for males = 5 ppm, based on bilateral hyperplasia and hypertrophy of the respiratory epithelium at 20 ppm at 1 year. NOEL for females = 20 ppm, based on hyperplasia and hypertrophy of the respiratory epithelium, epithelial hyperplasia of the urinary bladder in females, and subacute to chronic inflammation of the urinary bladder in females. Body weights were typically marginally reduced after 6-12 months (usually not statistically significant). This is a valid supplement to the oncogenicity study (original review was by F. Martz, 1/14/86), re-examined by Aldous in conjunction with a risk assessment (1/27/15).

50046-097 140561 Redmond, J. M., K. E. Stebbins and W.T. Stott, "Telone*II Soil Fumigant: Two-year dietary chronic toxicity/oncogenicity study in B6C3F1 Mice - Final Report", The Toxicology Research Laboratory, The Dow Chemical Co., Midland MI. Aug. 9, 1995. Study ID M-003993-032. Microencapsulated Telone*II, purity 95.8% 1,3-dichloropropene (50.7% cis/45.1% trans), was admixed with the diet at concentrations of 0, 2.5, 25, or 50 mg/kg/day and fed to 50 B6C3F1 mice/sex/group for 24 months. Additional mice (10/sex/group) were allocated for a 1-yr interim sacrifice. NOEL = 2.5 mg/kg/day (body weight decrements, both sexes). Upper dose levels achieved, but did not exceed, an MTD. The most definitively treatment-related effect was decreased hepatocyte size in 6/10 of the 50 mg/kg/day males at 1-yr sacrifice. There was a small increase in high dose females with stromal cell sarcomas, originating in the cervix or uterus, compared to concurrent controls (one control vs. four high dose females). In the 1996 DPR review, this was considered as a "possible adverse effect", and histopathological examinations of cervix or uterus slides of intermediate groups were requested, in addition to relevant historical control data. The requested data were submitted (Document No. 50046-103, Record # 151706). Stromal cell sarcoma incidence was 1, 0, 1, and 4 in controls through high dose groups. Historical control incidence of combined uterine or cervical stromal cell sarcomas ranged from 0 to 4, with 4/16 studies having either 3 or 4 such tumors out of 50 mice. **No adverse effect: data do not indicate a treatment effect on tumor incidence. The study is now **acceptable as an oncogenicity study** (absence of blood chemistry precludes acceptance as a "combined" study). Aldous, 4/17/96, 3/10/97.

50046-072 126521 This 75-page interim report relates to Record # 140561 above. There are no essential data unique to this interim report. Aldous, 7/15/99.

50046-0240 291162 Kelly, C. M., "An oncogenicity study with DD-92 in the mouse via oral gavage administration," Huntingdon Life Sciences, East Millstone, NJ, 12/17/97. Laboratory Study # 95-2378. This was designated by Dow as a "Non-GLP Study." This is a 54-page report containing only one page of tabular summary findings, without individual data, entirely limited to findings in urinary bladder. CD-1 mice, 65/sex/group, were dosed daily by gavage with 0, 2, 10, or 25 mg/kg/day 1-3-dichloropropene (98.4% purity) in corn oil vehicle (5 ml/kg b.w.) for 18 months. No in-life changes were reported. The only clear histopathology response was in 25 mg/kg/day females, and was limited to urinary bladder, with the following incidences (out of

65): hyaline change (38), hyperplasia of transitional epithelium (43), subacute (chronic active) or chronic inflammation (45), stromal hyperplasia (11), and brown pigment accumulation in reticuloendothelial cells (7). All of the above compared with incidences of 0 or 1 out of 65 in female controls, hence highly significant. Males were only marginally affected, with a slight increase in hyaline change (6/65, compared to none in controls). Three high dose females displayed benign submucosal mesenchymal tumors, compared to none in other groups. Investigators justifiably attributed these tumors to treatment. Investigators noted that these tumors arose from regions of the above predisposing lesions, that were likely secondary to sustained local irritation, that the tumors were small in size and did not appear to be invasive, that all three tumors arose late in the study or at termination, and that this tumor type may be more common than reported due to technical features of routine sectioning. Investigators concluded that there were no other treatment-related neoplasia, but this report did not give incidence data of other tissues for DPR review. Report is designated as supplementary data. Aldous, July 31, 2016.

Various mouse oncogenicity studies: non-guideline exposure protocols

50046-010 036553 "Toxicology and Carcinogenesis Studies of Telone II in F344/N Rats and B6C3F1 Mice." (NTP Technical Report Series No. 269, Frederick Cancer Research Center, 5/85). **This 1-liner summarizes results in mice**. Telone II (1,3-dichloropropene, 87.5% pure, with epichlorohydrin as stabilizer) was administered to 50/sex/group at 0, 50, or 100 mg/kg by oral gavage "3 times a week" for 104 weeks. Study is scientifically valid but unacceptable and not upgradeable because it was not designed to address FIFRA guidelines. Also, 25 control male mice died mid-study from myocarditis, compromising the usefulness of this group. **Urinary bladder** was a target organ, with primary non-neoplastic lesion of epithelial hyperplasia incidence (out of 50) in control through high dose males of 0, 9, and 18, and in females of 2, 15, and 19. Urinary bladder incidence of transitional cell carcinoma was 0, 0, and 2 for corresponding males, and 0, 8, and 21 in females. **Lungs** did not show pre-disposing non-neoplastic change, but there were increases in alveolar/bronchiolar tumor incidences as follows: control to high dose male adenoma incidences of 1, 11, and 9, respectively; and 0, 3, and 8 in females; corresponding carcinoma incidences were 0, 2, and 3 in males; and 2, 1, and 0 in females. **Forestomach** hyperplasia incidence was 0, 0, and 4 in males; and 1, 1, and 21 in females. Forestomach squamous cell papilloma incidences were 0, 2, and 3 in males; and 0, 1, and 2 in females. Forestomach squamous cell carcinoma was observed only in 2 high dose females. Study is not acceptable, due to compromised control male survival (above) and to technical problems in design. Above tumors and pre-disposing lesions are "possible adverse effects." Original review was by Martz, 1/17/86, with a revision of this summary without a new worksheet by Aldous, 1/30/15.

NOTE: Document No. 50046-010, Record No. 036554 refers to the same published article in JNCI 63 cited in Document No. 50046-007, Record Nos. 028361-028363. Multiple record numbers in Document No. 50046-007 represent 3 different dosing protocols presented in the publication, none of which approached guideline procedures. Aldous, 4/22/96.

50046-010 036554 "Carcinogenicity of Halogenated Olefinic and Aliphatic Hydrocarbons in Mice." (Van Duuren, B. L. et al., NYU Med Center, JNCI 63: 1433-1439, 1979) Ha:ICR Swiss strain; cis-1,3-dichloropropene (Chemical Samples Co., Columbus, OH), 122 mg/mouse or 41 mg/mouse by dermal application 3/week for about 77 weeks; initially reviewed as having caused

no local or distant tumors. UNACCEPTABLE and not upgradeable. Reviewed: 6/3/85 by Apostolou, peer review 2/20 and 8/18/86 by Martz. Re-review as part of the risk assessment process noted that the incidence of lung tumors in both groups of treated mice was statistically significant by Fisher's Exact Test although not so noted in the publication table. The incidences were 30/100 for controls and 19/30 and 17/30 at low and high doses respectively. Study remains UNACCEPTABLE but with a possible adverse effect. (Gee, 5/31/90).

50046-007 028361 (same publication as 036554, above, refers to the repeated dermal cis-1,3-dichloropropene treatments).

010 036554 "Carcinogenicity of Halogenated Olefinic and Aliphatic Hydrocarbons in Mice." (NYU Med Center, JNCI 63: 1433-1439, 1979) Ha:ICR Swiss strain; cis-1,3-dichloropropene (Chemical Samples Co., Columbus, OH), 3 mg/mouse once weekly x 77 weeks by subcutaneous injection; examined injection site and liver only; fibrosarcoma at injection site, 6/30 vs. 0/30 vehicle control, probably due to irritation by physical-chemical properties of A.I. Otherwise, insufficient for assessment. UNACCEPTABLE and not upgradeable. (Apostolou, 6/3/85; Martz 2/20 and 8/18/86).

50046-007 028362 (same publication as 036554, above, relating to subcutaneous cis-1,3-dichloropropene treatment). Reviewed under this record number by Apostolou (see above).

010 036554 (suppl. to 028363) "Carcinogenicity of Halogenated Olefinic and Aliphatic Hydrocarbons in Mice." (NYU Med Center, JNCI 63: 1433-1439, 1979) Ha:ICR Swiss strain; cis-1,3-dichloropropene (Chemical Samples Co., Columbus, OH), 122 mg/mouse by a single dermal application, followed by promotion with 5 mg phorbol myristate acetate (PMA) dermally 3/week for about 77 weeks; no significant increase in tumors due to the a.i. [4/30 with dermal papillomas in cis-1,3-dichloropropene group: 6/90 in PMA positive control group: 0/100 in untreated mice, and evidently 0/30 in acetone (sham promoter) treatment group]. UNACCEPTABLE and not upgradeable. (Reviewed: 6/3/85 by Apostolou, peer review 2/20 and 8/18/86 by Martz).

50046-007 028363 (relates to investigation using single dermal application of cis-1,3-dichloropropene plus PMA promotion in Record No. 036554, above: originally reviewed under this record number by Apostolou).

GENOTOXICITY

Bacterial reverse mutation assay ** † (positive studies may not represent modern Telone II a.i.)

The series of genotoxicity studies submitted for 1,3-dichloropropene contains many positive studies and many negative studies. The positive studies tend represent older formulations of technical 1,3-dichloropropene (typically pre-1980), whereas negative studies are typically several years more recent. Usually Ames test studies which indicate positive bacterial mutagenicity responses found base-pair substitution mutants rather than frameshift alterations

(i.e. tests show increased revertants in TA 1535 and TA 100 strains, compared to little or no response in strains TA 98, TA 1537, or TA 1538). Usually the presence or absence of S-9 has little to do with mutagenicity. Providing human liver physiological levels of glutathione (GSH) typically greatly suppresses mutagenicity. Many supplementary studies relating to oncogenicity and mutagenicity are found below beginning with the section on "Mechanistic Studies," below. Aldous, 6/22/15.

50046-016, **004282** & 004293 "Mutagenicity of 1,3-Dichloropropene using Ames Testing." (Schering AG, summary report 9/82) Formulated mixtures containing 1,3-dichloropropene in addition to various other constituents, were tested for mutagenic activity in the Ames Salmonella Test. Results were conflicting and insufficient for independent assessment. UNACCEPTABLE but upgradeable upon submission of complete report(s). Summary contains statement that positive effects were seen with TA1535 and TA100 but no data. Report contains a statement that the methyl isothiocyanate in the sample tested caused cytotoxicity before the mutagenic effect was detectable. No data. (Reviewed: 6/3/85 by Apostolou, peer review 8/18/86 by Martz and 7/18/88 by Gee).

Note by Aldous (4/20/15) relating to the above Schering AG study: the test article in this study was designated as "D-D," a mixture of "C_3 hydrocarbons including dichloropropenes, dichloropropene and related chlorinated hydrocarbons." This mixture constituted 80% of a formulation called Vorlex II, which is not currently registered in California. This test article differs appreciably from modern Telone II. The NTP report of rat and mouse oncogenicity studies reported in 50046-0010, Record No. 036552 and 036223, describes D-D as a synonym of *cis, trans*-1,3-dichloropropene, as found in Telone and Vorlex Soil Fumigant products. The latter record specifies components of the technical test article as including 89% *cis, trans*-1,3-dichloropropene, 1.5% of a trichloropropene isomer, 2.5% 1,2-dichloropropane, and most importantly, 1.0% epichlorohydrin. Technical Telone II from a more recent assay (Sept. 1999) was comprised of 97.5% *cis, trans*-1,3-dichloropropene, with lesser amounts of trichloropropene isomers and of 1,2-dichloropropane, and no epichlorohydrin. It is unclear to what extent contaminants in older technical 1,3-dichloropropene may have affected the mutagenicity tests.

50046-0010 036556 "Mutagenicity of 1,3-Dichloropropene in Bacteria Test System." (Nomura Sogo Res. Inst., 12/78) E. coli strain B/r, Wp 2, Try^-; 49.8%-cis and 46.3%-trans 1,3-dichloropropene, 5000, 2500, 1000, 500, 250, 100, 25, or 0 µg/plate, ±S9. Unacceptable and not upgradeable due to design deficiencies. No mutagenic effects were reported. (Gee, 2/24/86).

50046-010 036558 "Mutagenicity of 1,3-Dichloropropene in Bacteria Test System." (Nomura Sogo Res. Inst., 12/78) Five Salmonella strains for plate assay; 49.8%-cis and 46.3%-trans 1,3-dichloropropene, 0-5000 µg/plate ± S9; G46 for host-mediated assay in ICR mice at 30 or 60 mg/kg x 3 times/3 hours. UNACCEPTABLE and not upgradeable: single plates. Significant **Positive response** in several strains indicative of base-pair substitution; negative in host-mediated assay. (Gee, 2/24/86).

Note (by Aldous, 4/21/15): there were > 10-fold increases in revertant colonies, particularly for *Salmonella typhimurium* strains TA 1535 and TA 100, with and without S-9. The report does not state whether this technical product contained epichlorohydrin. This study was of the same time period as the NTP studies in rats and mice, which tested an old formulation technical 1,3-dichloropropene containing 1% epichlorohydrin. See Document No. 50046-010, Record Nos.

036552 and 036553, "Toxicology and Carcinogenesis Studies of Telone II in F344/N Rats and B6C3F1 Mice."

(No DPR Document or Record Number) De Lorenzo, F., S. Degl'Innocenti, A. Ruocco, L. Silengo, and R. Cortese, "Mutagenicity of pesticides containing 1,3-dichloropropene," Cancer Research 37:1915-1917 (June 1977). Investigators reported that an old technical formulation of Telone elicited several-fold increases in revertants over controls in point mutation-associated Salmonella strains TA 1535 and TA 100, and also in TA 1978 (described as similar to TA 1538, but with a normal DNA-excision repair system). Investigators also tested individually the *cis*- and *trans*- isomers of 1,3-dichloropropene, reporting roughly 50-fold increases in mutant colonies with and without S9 in TA 1535, roughly 20-fold increases with and without S9 with TA 100, and about 4-fold increases with TA 1978: all of these maximum responses were in the range of 50 to 100 µg/plate. In addition to the major Telone ingredients, investigators also evaluated 2,3-dichloro-1-propene, which elicited responses similar to the Telone isomers, and 1,2-dichloropropane, which was about 1000-fold less potent than the Telone isomers. This was a 3-page report, with no evident quality assurance protocols and no individual data to validate reported results. As such, there is no DPR worksheet. One-liner is by C. Aldous, 4/22/15.

Mutagenicity: *In vitro* mammalian cell assay **

Summary: Typically mammalian cell studies have been negative. Some older positive bacterial studies have been reported. There are no recent, standard Ames tests employing modern formulation Telone® II (which does not have mutagenic epichlorohydrin as stabilizer). This is important, because older studies (such as Record No. 036558) which were positive did contain epichlorohydrin. One problem is the volatility of the test material and care must be taken to control samples for this property. From the text of the study with CHO, the flasks were tightly capped and loss of test material should not have been a factor. Overall, as of 9/10/99, there is considered to be a possible genotoxic effect in bacteria unless there are more recent studies using the current test article. Gee, 7/18/88 and 9/10/99.

** 019 042945 "The Evaluation of Telone II Soil Fumigant in the CHO Cell/HGPRT Forward Mutation Assay." (Dow, 2/27/86) CHO/HGPRT assay; Telone II (48.9% cis and 43.2% trans 1,3-dichloropropene); 250, 200, 150, 100, 50, or 0 mM without S9 (3 trials) and 200, 150, 125, 100, 50, or 0 mM with S9 (1 trial). Report complete and study ACCEPTABLE. NO evidence of mutagenicity. (Gee, 7/24/86).

Mutagenicity: *In vivo* cytogenetics **

** 010 036560 "Evaluation of Telone II Soil Fumigant in the Mouse Bone Marrow Micronucleus Test." (Dow, 5/85) Telone II (49.5%-cis and 42.6%-trans 1,3-dichloropropene), 380, 115, 38, or 0 mg/kg by oral gavage in CD-1 mice, 5/sex/group, 24 or 48 hour sacrifice. Reviewed 2/25/86 as incomplete but upgradeable with justification of the use of only two sacrifice times. This has been submitted as Record #55630 in 50046-025, based on excretion of 93% within 48 hours. The study is now reviewed as ACCEPTABLE. NO increase in micronucleated PCE's reported. (Gee, 2/25/86 and 4/16/87).

**50046-115 162466 Gollapudi, B. B., F. S. Cieszlak, and S. J. Lick, "Telone* II soil fumigant (cis/trans 1,3-dichloropropene): inhalation dominant lethal mutagenicity study in the CD

(Sprague-Dawley derived) rat", The Dow Chemical Co., Midland, 5/29/97. Laboratory Project Study ID 960035. Thirty male Crl:CD®(SD) rats per treatment group were dosed by inhalation for 6 hr/day, 7 days/wk, 10 weeks duration at levels of 0, 10, 60, and 150 ppm. Negative pair-fed controls (matched to food consumption of high dose rats) and positive controls (single oral dose of cyclophosphamide given 48 hr prior to first mating period) were not housed in inhalation chambers. Each of these male treatment groups consisted of 30 rats. There were two consecutive mating periods of 1 week each during weeks 11 and 12 (1 male/2 females). On day 13 after the end of respective mating periods, females were euthanized. Corpora lutea were counted, and uteri were examined for numbers of live implants and resorption sites. Uteri of apparently non-pregnant females were stained with sodium sulfide and examined for possible early resorptions. The NOEL for "subacute" change = 10 ppm (decreased food consumption and decreased body weight, particularly during the first week of treatment). There was no evidence of a dominant lethal effect (no increase in resorptions). **Acceptable, with no adverse effects**. Aldous, 8/18/99.

Mutagenicity: DNA Damage, or uncommon study designs ** †

Summary: Different tests measure different endpoints so no one conclusion can be reached. A possible adverse genotoxic effect is noted. As was the problem with point mutation studies above, older investigations employing mutagenic epichlorohydrin as stabilizer may not be relevant to evaluation of modern formulation Telone® II. Gee, 7/18/88 and 9/10/99.

** 010 036559 "Evaluation of Telone II in the Rat Hepatocyte Unscheduled DNA Synthesis Assay." (Dow, 4/85) UDS in rat hepatocytes; Telone II (49.5% cis and 42.6% trans-1,3-dichloropropene) $1x10^{-7}$ to $3x10^{-3}$ M concentration (solubility limit), plus control. Report complete and study ACCEPTABLE. NO evidence of UDS even when cytotoxicity was noted. (Gee, 2/24/86).

010 036557 "Mutagenicity Test on 1,3-Dichloropropene in Bacteria Test System." (Nomura Sogo Res. Inst., 12/78) Bacillus subtilis rec assay, strains H17 and M45; 49.8% cis- and 46.3% trans-1,3-dichloropropene, 1250, 500, 125, 50, or 0 mg/well without activation. UNACCEPTABLE and not upgradeable due to design deficiencies. **Slight growth differences at highest level.** Reviewed 2/24/86 by Gee. See also 1-liner for study 50046-010 036558, above, noting the likelihood epichlorohydrin in technical product of that time period.

50046-119 162470 Stott, W. T., T. J. Miller, and A. K. Wardynski, "1,3-Dichloropropene: *in vitro* DNA binding", The Dow Chemical Co., Midland, 12/12/97. Laboratory Project Study ID 970180. The study evaluated adduct formation when ^{14}C-labeled test material was incubated with calf thymus DNA solution with appropriate co-factors. Functional positive controls were ^{14}C-methyl iodide (without S9) and ^{14}C-1,2-dichloroethane (with S9). ^{14}C-1,3-dichloropropene did not elicit binding with or without S9. Useful ancillary data. The study does not address FIFRA data requirements, and was not performed under QA oversight. Aldous, 9/23/99.

50046-111 161850 Exact duplicate of 50046-119 162470, above.

Note: The reregistration standard of 1986 noted requirements for in vitro/in vivo primary hepatocyte UDS testing both in vitro and in vivo exposure - species not specified. Record # 036559 is not cited. (Gee, 5/23/89).

No record number "Chemical Mutagenesis Testing in Drosophila. III. Results of 48 Coded Compounds Tested for the National Toxicology Program." (Valencia, R., Mason, J. M., Woodruff, R. C., and Zimmering, S., Environmental Mutagenesis 7: 325 - 348 (1985)) 1,3-Dichloropropene technical, 95.5% was tested with male Canton-S wild-type stock by feeding at 5,570 ppm for 72 hours from soaked filter paper. The males were mated to Basc females for 3, 2 and 2 days. No more than 40 females per parental male were mated from each brood. A total of 6584 tests were performed. The percent lethals were 0.12 for control broods and 0.30 for treated broods - **considered positive by the authors.** The translocation test was negative. No worksheet. [Review was done in connection with the risk assessment.] (Gee, 5/31/90).

50046-120 162475 Gollapudi, B. B. and Cieszlak, F. S., "Telone® II Soil Fumigant: Evaluation in an *in vivo* assay for gene mutagens using transgenic Big Blue Mice," The Dow Chemical Co., Midland, 2/10/97. Laboratory Study # K-006409-017. Male Big Blue B6C3F1 mice, 5/group, were dosed by inhalation at 0, 10, 60, or 150 ppm of Telone II® Soil Fumigant, 96% purity, for 10 exposures (5/week over 2 weeks), at 6 hours/day. After an additional 17-day expression period, mice were killed. Each cell of the test mouse had about 40 copies of a shuttle vector carrying the *lacI* gene, the *lacI* promotor, the *lacI* operator, and the *αlacIZ* reporter gene. Mouse tissues (lung and liver) were homogenized, and the DNA was collected, digested, and packaged into phage particles using a proprietary system. The packaged DNA was added to plates containing the *E. coli* host bacteria. Following incubation, investigators counted the numbers of blue plaques compared to the total numbers of plaques as an index of mutations of the *lacI* gene. Blue plaques occur when a defective repressor protein allows transcription of the reporter gene, the product of which cleaves a chromogenic substrate (X-gal) in the medium. Only controls and 150 ppm mice were evaluated. Results showed no increases in mutations in lung or liver. Functional positive control tissues evidently derived from a single mouse, which was treated with five daily doses of 15 mg/kg/day diethylnitrosamine in water 54 weeks before sacrifice. NOEL for general toxicity = 60 ppm: all 150 ppm mice showed "decreased activity" during days 3-5 and days 8-12. There were no clinical signs observed at any other dose level. Body weights were not affected. Study is **not acceptable but is upgradeable** (DPR review notes concern about positive control). Aldous, 9/23/99, and again by Aldous on Jan. 8, 2015 (for minor additions to 1-liner to highlight subacute effects).

50046-111 161855 Exact duplicate of 50046-120 162475, above.

REPRODUCTIVE TOXICITY, RAT **

**50046- 030 060676 Breslin, W. J., H. D. Kirk, C. M. Streeter, J. F. Quast, and J. R. Szabo, "Telone II Soil Fumigant: Two-Generation Inhalation Reproduction Study in Fischer 344 Rats." (Dow Chemical, 7/13/87, M-003993-015). Thirty rats/sex/group received 1,3-dichloropropene, 91.2%, lot #TB831213-4, by inhalation at 0, 10, 30 or 90 ppm for 5 days/week during pre-mating periods, and for 7 days/week during mating, gestation, and lactation periods. This treatment schedule was continuous except that gravid females were not dosed from presumed gestation day 20 until lactation day 4. There were two generations with two littering periods each. Pups were not directly exposed, but were separated from dams for the 6-hour maternal exposures. Parental NOEL = 30 ppm, based on decreased adult body weights (commonly statistically significant in males and occasionally significant in females), and nasal histopathology (slight hyperplasia of

the respiratory epithelium in the majority of adults, and degeneration of the olfactory epithelium in many adults at 90 ppm). Reproduction NOEL ≥ 90 ppm (no adverse effect on reproduction parameters). Acceptable. (Gee, 7/13/88, with a re-examination that did not make major changes to the 1-liner, with no new worksheet, by Aldous on Jan. 8, 2015).

010 036555 "D-D: A 10 Week Inhalation Study of Mating Behavior in Male and Female Rats." (Shell (UK), 4/80) Wistar strain; technical D-D ("epichlorohydrin free"), 53.7% 1,3-dichloropropene, remaining constituents mainly chlorinated isomers/analogs; 96, 32, 14, or 0 ppm for 6 hours/day x 5 days/week; treated males mated with naive females after 2, 4, 7, and 10 weeks exposure; treated females mated with naive males after 10 weeks exposure; hematology, serum chemistry, urinalysis, and histopathology on satellite animals; 30 males and 24 females per group with 20 and 15 respectively for reproduction performance and the remainder for hematology, etc. UNACCEPTABLE and not upgradeable: only 1 generation and inadequate group sizes. Otherwise, appears to be a well conducted and documented study with scientifically valid results. NO reproductive effects. Liver and kidney weight elevation at 96 ppm, reversible upon withdrawal, except female kidney values. (Martz, 2/20/86) (Report is apparently identical to Document No. 50046-013, Record No. 932846).

DEVELOPMENTAL TOXICITY

Rat Developmental Toxicity**

50046-0010 036561 John, J. A., P. M. Kloes, L. L. Calhoun, and J. T. Young, "Telone* II: Inhalation teratology study in Fischer 344 rats and New Zealand White rabbits," The Dow Chemical Company, Midland, MI, 10/31/83. [Rat and Rabbit data were presented together in this report: the present DPR review is confined to the **rat.] Thirty mated female F344 rats were dosed with Telone II (1,3-dichloropropene; 90.1% pure: 47.7% *trans* and 42.4% *cis* isomers) by whole-body inhalation at 0, 20, 60, or 120 ppm for 6 hrs/day on gestation days 6-15 in a developmental toxicity study. A review by Martz (2/21/86) found study to be **acceptable, with no adverse effects**, setting the maternal effects NOEL at less than 20 ppm, based on reduced maternal body weight gain associated with reduced food consumption at all dose levels. Martz attributed a modest increase in delayed ossification of vertebral centers at 120 ppm to treatment, justifiably attributing this to maternal toxicity (body weight loss). The noted change in ossification delay in vertebral centra (affecting 6/27 control and 12/24 high dose litters) was not statistically significant. This places the NOEL for developmental response at 60 ppm. This study was re-examined by Aldous in 2015 to re-examine the basis of the NOEL. Re-examination confirms that there is no maternal NOEL (NOEL < 20 ppm): food consumption was reduced with linear dose-response throughout the treatment period in all treatment groups. Maternal body weight gain underwent a modest but statistically significant decrement at onset of dosing (gestation days 6-8) at 20 ppm. Maternal body weight gain was significantly reduced in 60 and 120 ppm dams during gestation days 6-11. Aldous, Jan. 8, 2015. (See pilot study, rat and rabbit, below.)

50046-0223 283293 Kloes, P. M., L. L. Calhoun, J. T. Young, and J. A. John, "Telone II: Inhalation teratology probe study in Fischer 344 rats and New Zealand White rabbits," The Dow Chemical Company, Midland, MI, March 30, 1983. Mated female rats and rabbits were dosed by whole-body inhalation for 6 hr/day at 0, 50, 150, or 300 ppm of Telone II (47.7% cis, 42.2%

trans, with impurities including 1.8 % epichlorohydrin) on gestation days 6-15 (rat) or 6-18 (rabbit). Scheduled sacrifices were on gestation days 16 (rats) or 19 (rabbits). RAT PHASE: There were 8, 7, 8, and 8 dams on study (control through 300 ppm groups), yielding 8, 7, 6, and 7 dams with litters at sacrifice. One high dose dam was found dead on gestation day 14: all others survived. Two of the eight 150 ppm dams had pregnancies that were only evident upon sodium sulfide staining of the uteri: this is unlikely to have been treatment-related, since the 300 ppm group had recognizable fetuses in all litters. Litters/[litters with resorption(s)] were 3/8, 3/7, 3/6, and 7/7 in control through high dose groups (statistically increased and likely dose-related at 300 ppm). Censoring the two mid-dose cases of sulfide-staining-only pregnancy detection, incidences of litters totally resorbed were 0/8, 0/7, 1/6, and 3/7, respectively. Treatment effect may be supposed for 300 ppm rats, whereas the single case at 150 ppm was equivocal [note that in the definitive developmental toxicity study (DPR Record No. 036561), 0/24 pregnant dams had total litter losses at the highest dose of 120 ppm]. Rat body weight gain decrements were evident at all dose levels, particularly during the first 2 treatment days. Body weight gains between gestation days 6 and 8 were 3.5, -4.5, -14.3, and -21.4 g in respective groups (statistically significant in all treated groups). Subsequent body weight gains were normal for 50 ppm dams, but body weight decrements continued for 150 ppm and especially for 300 ppm dams, with net body weight gains of 26, 13, -9, and -51 g in respective groups. Food consumption during the first 3 treatment days was unaffected at 50 ppm, but markedly reduced at 150 and 300 ppm (13, 13, 9, and 3 g/rat/day). Reduced food consumption was evident through gestation day twelve at 150 ppm and throughout the study at 300 ppm. There were no tabulated clinical signs data in this study, but investigators observed that "rats exposed to 300 ppm of TELONE II were observed to have urine and fecal staining as early as day 8 of gestation. Nasal exudate and red crusty material around the eyes were observed in this group intermittently until necropsy on day 16 of gestation." No clinical signs were evident in 50 or 150 ppm dams. RABBIT PHASE: There were 7 mated does/group on study, yielding 6, 7, 6, and 0 does with litters at sacrifice (one control was not pregnant, one 150 doe died of a bacterial pneumonia evidently unrelated to treatment, and all six pregnant 300 ppm does died). Investigators found no clinical changes in 50 or 150 ppm does, however "Six of 7 rabbits exposed to 300 ppm of TELONE II, however, showed signs of toxicity such as rear limb ataxia, decreased or absence of righting reflex and flaccid hind limb muscles. These animals were either sacrificed moribund or found dead within 24 hours of onset of these signs. Onset of these signs occurred between gestation days 14 and 19." Body weights were not affected at 50 ppm, but were decreased at 150 ppm only (body weight gain during treatment phase was 18, 17, and -202 g for control through 150 ppm respectively: with no 300 ppm females surviving to termination). There were no treatment effects at gestation day 19 examination of fetuses of 50 or 150 ppm does, with no pregnant surviving does at 300 ppm. Useful supplementary data (pilot study), Aldous, 3/13/15. (Note: Record No. 283292 is an electronic submission of the present record.).

Rabbit Developmental Toxicity**

**50046-0010 036562 John, J. A., P. M. Kloes, L. L. Calhoun, and J. T. Young, "Telone* II: Inhalation teratology study in Fischer 344 rats and New Zealand White rabbits," The Dow Chemical Company, Midland, MI, 10/31/83. [Rat and Rabbit data were presented together in this report: the present DPR review is confined to the rabbit.] Twenty-five to 31 inseminated New Zealand White rabbits were dosed with Telone II (1,3-dichloropropene; 90.1% pure: 47.7% *trans* and 42.4% *cis* isomers) by whole-body inhalation at 0, 20, 60, or 120 ppm for 6 hrs/day on gestation days 6-18 in a developmental toxicity study. There were 24, 18, 17, and 21 does with

viable litters at C-section, considered to be sufficient for evaluation. There was no evidence of reduced maternal viability or of altered developmental outcomes. The initial review by Martz (2/21/86) requested historical control data on soft tissue alterations as a condition of acceptance. Those data were provided in Document 50046-025, Record No. 50619. Upon receipt of the new information, Martz determined that this study is acceptable, with no adverse effects (3/26/87). Martz determined that the NOEL was 20 ppm for reduced maternal weight gain. This study was re-examined by Aldous in 2015 to re-examine the basis of the NOEL. The new examination noted some deficiencies in this study compared to modern developmental toxicity studies, but the study remains acceptable. Examination of the individual body weight gain data shows that the evidence of decrements in maternal body weight gain during the first 3 days of dosing is equivocal. Study authors had concluded that the small body weight decrements during gestation days 6-8 at 60-120 ppm were plausibly treatment-related. The Aldous re-examination does not change the NOEL, but acknowledges that apparent body weight changes were small and lacking in dose-response. Aldous, Jan. 8, 2015. (See pilot study, rat and rabbit, above.)

NEUROTOXICITY (Hen studies are not currently required)

Acute neurotoxicity, rat
No study submitted.

90-day neurotoxicity, rat
No study submitted.

Developmental neurotoxicity, rat
No study submitted.

Delayed neurotoxicity, hen
No study submitted.

IMMUNOTOXICITY
No study submitted.

ENDOCRINE DISRUPTOR STUDIES
No study submitted.

APPENDIX
The Appendix includes published and unpublished studies. Often the published studies do not contain individual data, and typically lack quality assurance validation, and thus are not amenable to DPR review worksheets. Entries without DPR Document numbers and Record numbers were typically not submitted by registrants. Studies in this section were not undertaken to fill FIFRA data requirements, and do not appear to indicate unique evidence of toxic hazards.

Collectively, these studies greatly enhance the understanding of mechanisms of toxicity beyond the scope of FIFRA-mandated protocols.

Mechanistic studies examined by DPR Data Review Group

50046-0026 058182 Dietz, F. K., E. A. Hermann, P. E. Kastl, D. A. Dittenber, and J. C. Ramsey, "1,3-dichloropropene: pharmacokinetics, effect on tissue non-protein sulfhydryls, and macromolecular binding in Fischer-344 rats and B6C3F1 mice following oral administration," The Dow Chemical Company, Midland, MI, March, 1985. This is a brief report of a relatively old study, without great detail, but useful primarily in addressing depletion of non-protein sulfhydryls (below). Most of the ^{14}C-1,3-dichloropropene (1,3-D) in this study was uniformly labeled, with isotope ratio of 62% *cis*, 38% *trans* (a single urinary elution profile from rats treated with purified labeled *cis* 1,3-D was similar to those derived from the labeled cis/trans mixture). Only male rats and mice were used. Percent of administered label recovered in 48-hr experiments following 1 mg/kg doses was: (rat) 51% in urine, 20% in feces, 18% in exhaled CO_2, and 6% in carcass; (mouse) 79% in urine, 16% in feces, 14% in exhaled CO_2, and 2% in carcass. Tissue distribution (µg equivalents) 48 hours following 1 mg/kg dosing was: (rats) about 0.2 to 0.3µg equiv. for non-glandular stomach, glandular stomach, liver, kidney, and bladder; (mice) 0.23 µg equiv. for non-glandular stomach, about 0.1 µg equiv. for bladder, liver, and kidney, and only 0.04 µg equiv. for glandular stomach. Estimated elimination $T_{1/2}$ for rats and mice was consistently about 5-6 hrs, regardless of dose (1 and 50 mg/kg tested for rats, and 1 and 100 mg/kg for mice). Chromatographic analysis of rat and mouse urine samples found 2 prominent urinary peaks for each species: one peak was shown by MS to be N-acetyl-S-(3-chloroprop-2-enyl) cysteine derivatives, and the other peak was presumed to represent derived sulfoxide and/or sulfone products. Low dose (1 mg/kg) rats produced comparable amounts of the two products. Higher dose rats (30 to 50 mg/kg) produced roughly 3-fold more of the N-acetyl-S-(3-chloroprop-2-enyl) cysteine than sulfoxide and/or sulfone products. High dose mice (100 mg/kg) produced slightly more of the sulfoxide and/or sulfone products compared to N-acetyl-S-(3-chloroprop-2-enyl) cysteine. As had been previously reported in an abstract (see DPR Document No. 50046-0015, Record No. 932856), there was substantial difference in depletion of non-protein sulfhydryls (NPS) between different tissues. Non-glandular stomach showed the greatest depletion (evidently meaningfully reduced at 5 mg/kg in both species), and with marked depletion at 50 to 100 mg/kg in both species. In both species, NPS content of kidney was unaffected, the bladder scarcely affected, and glandular stomach and liver showed depletion to an intermediate degree. A time-course evaluation of NPS contents of these tissues in 100 mg/kg mice found complete recovery of NPS content in non-glandular and glandular stomach over the time frame of 4 to 8 or 12 hours after dosing. Liver, although never as profoundly depleted of NPS as the non-glandular or glandular stomach, required between 8 and12 hours to show recovery. Particularly the evidence that high doses of 1,3-D depletes NPS such as glutathione in non-glandular stomach may be relevant evidence for a threshold for tumors in this organ. Aldous, 1/30/15.

50046-120 162472 Lawlor, T. E., "Evaluation of 1,3-dichloropropene for mutagenic potential in *Salmonella* in the presence of mouse lung homogenate (S9)", Corning Hazleton Inc. (CHV), 11/26/96. CHV Study ID No. 17037-0-401. *Salmonella typhimurium* TA 100 was the only strain employed in this supplemental mutagenicity study, which evaluated the effects of S9 from mouse lung homogenate and of supplementary GSH in Ames-style reverse mutation plate assays following a 20-minute pre-incubation period in sealed tubes. S9 preparations were prepared

from B6C3F1 mice: either controls, or exposed to 1,3-dichloropropene by inhalation (63 ppm, 5 days/wk, 2.5 wks). Preliminary tests with mouse lung S9 preparations with positive control substances benzo(a)pyrene and 2-aminoanthracene found that only the latter increased revertant incidence with mouse lung S9 mix. In studies with mouse lung S9 (whether derived from controls or from 1,3-dichloropropene-treated mice, in either case with or without GSH) there was no increase in revertants due to 1,3-dichloropropene treatment over the survivable range of 75 to 300 µg/plate. Studies without S9 similarly showed no treatment effect throughout the meaningful range. Cytotoxicity was evident between 300 and 600 µg/plate with S9. Studies without S9 found no cytotoxicity at 300 µg/plate, but severe cytotoxicity at 450 µg/plate. Results were thus negative under conditions of study (single strain, single trial, three reps/dose level), suggesting that mouse lung microsomal enzymes did not elicit previously-indicated responses by metabolizing 1,3-dichloropropene to a mutagenic intermediate. Useful supplementary data. Aldous, 9/21/99.

50046-111 161852 Exact duplicate of 50046-120 162472, above.

50046-119 162471 Stott, W. T., B. B. Gollapudi, C. M. Clements, V. A. Linscombe, D. A. Dittenber, S. J. Lick, and K. A. Johnson, "1,3-Dichloropropene: mechanism of tumorigenicity studies in male B6C3F1 mice and Fischer 344 rats", The Dow Chemical Co., Midland, 12/12/97. Laboratory Project Study ID # 971121. Hepatocellular tumors were noted in male F344 rats administered microencapsulated Telone in the diet (Record No. 140562), and benign lung bronchioalveolar adenomas were previously found in male B6C3F1 mice in an inhalation study (Record No. 060675). The present study sought to determine whether Telone is mutagenic or otherwise likely to have elicited such tumors by any of several means evaluated, including: (1) cell proliferation studies: evaluated by analysis of BrdU uptake in target tissues, with nuclear labeling visualized by immunohistochemical methods, (2) apoptosis: evaluated by using antibodies to the exposed 3'-OH ends of DNA fragments (which are characteristic of apoptosis), followed by antibody binding, then by addition of a chromophore to the antibody constituents, allowing quantitation by light microscopy (3) Glutathione (GSH) was evaluated from rat liver and mouse lung homogenates by a clinical chemistry analyzer (in addition to sacrifices of animals exposed continuously up to the time of sacrifice, some rats and mice were killed about 24 hr after the last exposure to assess "rebound" recovery of GSH in tissues), (4) DNA adduct formation was evaluated by a ^{32}P-post-labeling assay, in which DNA was isolated, digested to release 3'-mononucleotides, enriched in certain fractions expected to contain adducts: these fractions were then labeled using T4 polynucleotide kinase and [γ-^{32}P]ATP, and finally treated with nuclease P1 to create labeled 5'-mononucleotides. Labeled adducts were then separated by 2-dimensional TLC. Chromatograms were compared to those produced by action of a known mutagen (propylene oxide) on DNA samples *in vitro*. NOEL's in rats and mice were 12.5 mg/kg/day and 10 ppm, respectively, based on reductions in GSH levels. NOEL's for outcomes more commonly considered to reflect toxicity, such as modest body weight decrements in both species and increased circulating ALT and AST in rats as indicators of liver responses, were 25 mg/kg/day and 60 ppm, respectively. Evidence of strong dose-response for depletion of GSH and increased turnover of GSH suggest that high dose effects may relate to depletion of natural detoxification capacity, indicating that high dose responses, including tumors, may have little or no relevance to chronic exposure at lower levels. None of the mechanistic studies identified treatment effects on cell proliferation, apoptosis, or DNA adduct formation. The authors

concluded that the tumors were caused by a non-genotoxic mode of action *in vivo*. Often, small sample sizes and large inter-animal variability limited the level of confidence in these "negative" results. Aldous, 9/23/99.

50046-111 161851 Exact duplicate of 50046-119 162471, above.

Schneider, M., Quistad, G. B., and Casida, J. E. 1998. "1,3-Dichloropropene epoxides: intermediates in bioactivation of the promutagen 1,3-dichloropropene," *Chem Res Toxicol* 11:1137-1144. The 92% cis/trans (1:1) 1,3-dichloropropene (1,3-D) obtained for this study contained 0.2% each of cis and trans epoxides, which could be quantitatively removed by DMSO at room temperature (i.e. degraded by this solvent without the need for added cofactors). The metabolic oxidation of epoxide-free 1,3-D [*cis*/*trans* (1:1)] to form respective epoxides was demonstrated in Swiss-Webster mice (700 mg/kg by intraperitoneal injection): liver extracts of these mice yielded several times more cis- epoxide than trans- epoxide. Peak epoxide levels were several hundred-fold lower than corresponding peak 1,3-D levels for *cis* or *trans* forms. Similarly, *in vitro* mouse liver microsomal preparations of epoxide-free 1,3-D in the presence of NADPH also yielded preferentially *cis* epoxide. When GSH in addition to NADPH were added to the same *in vitro* system, there were markedly reduced *cis* and *trans* epoxide levels, and respective parent 1,3-D levels in liver extracts were reduced to about 30% of respective isomer levels of microsomal preparations lacking NADPH and GSH. Potential metabolites sought but not found in this assessment were 2-chloroacrolein and cis- and trans- 3-chloroacrolein. *In vivo* treatment of mice with either purified *cis*- or *trans*-1,3-D yielded only the corresponding *cis*- or *trans*- epoxide in extracted liver. Liver levels of *cis*- or *trans*- 1,3-D and corresponding epoxides were assessed following a single ip dose of 700 mg/kg of 1,3-D at a 1:1 cis:trans ratio. Of parent compounds, the *trans*- 1,3-D levels predominated (roughly 2-fold) over *cis*-1,3D throughout the 150 minute sampling period. In contrast, *cis*- 1,3-epoxide predominated over the *trans*-epoxide in liver extracts by about 2-fold during that period. Cis/trans 1,3-D epoxides dissolved in DMSO yielded a virtually quantitative product of 2-chloroacrolein within 280 minutes at 22°C, with 2,3-dichloropropanal as an intermediate product. Cis/trans 1,3-D epoxide decomposition in pH 7.4 buffer yielded predominantly 3-chloro-2-hydroxypropanal (including its dimer). Whereas both epoxides degraded spontaneously in pH 7.4 buffer, addition of GSH roughly doubled degradation rate, and GSH plus glutathione S-transferase (GST) increased the latter rate about 60-fold. In contrast, 2-chloroacrolein (not detected in this study under physiological conditions) degraded only slowly in buffer alone, but decomposed too rapidly to quantify upon addition of GSH, with or without GST. Rat liver microsomal epoxide hydrolase and soluble epoxide hydrolase activities, when expressed in insect cells, were examined for inhibition by cis/trans-1,3-D epoxides of activity toward tritiated cis-stilbene oxide. When 1 mM solutions of cis/trans-1,3-D epoxides were incubated for various time periods prior to addition of cis-stilbene oxide in the presence of rat liver **microsomal** epoxide hydrolase, there was about 60% inhibition of cis-stilbene oxide hydrolase activity at time 0, with a decline to zero inhibition after 10 minutes. When 1 mM solutions of cis/trans-1,3-D epoxides were incubated for various time periods prior to addition of labeled trans-stilbene oxide in the presence of rat liver **soluble** epoxide hydrolase, the trans-stilbene oxide hydrolase activity inhibition peaked in 5 minutes at 50% inhibition, with about 35% inhibition remaining at the final sampling time of 20 minutes. **Microsomal** epoxide hydrolase is associated with many xenobiotic responses. Mutagenicity by standard plate incorporation method in *S. typhimurium* TA 100, a system previously shown respond to technical

Telone, found mutagenicity of 1,3-D (cis) to be at least 4 orders of magnitude less potent than either of the 1,3-D epoxides (trans 1,3-D was not tested here). A very small positive value reported for 1,3-D (cis) **with** S9 activation was considered to represent a treatment effect by investigators. Both epoxides elicited revertant responses, with cis-epoxide about 2x more potent than trans-epoxide. As observed in other studies, S9 had no effect on mutagenicity of either of the epoxides. 2-Chloroacrolein was about 4x more potent than cis-1,3D epoxide. In contrast, 3-chloroacrolein (also not shown here to be a metabolite of 1,3-D under physiological conditions) was a very weak direct mutagen, about the same potency as cis-1,3-D. Varying GSH from 0 to 5 mM in TA 100 plate incorporation tests employing cis- and trans-epoxides (without GST) yielded a log-linear decrease in revertants over the entire range tested, although the cis-epoxide retained some mutagenicity even at the highest GSH level. Under these conditions, 2-chloroacrolein showed roughly constant mutagenicity between 0 and 0.25 mM GSH, with mutagenicity diminishing to about 25% of maximum levels at 5 mM GSH. In the latter test series, with cis- and trans-epoxides and with 2-chloroacrolein, addition of glutathione S-transferase either had no effect or decreased mutagenicity for each GSH level. In conclusion, investigators proposed that "the penultimate and ultimate mutagens of 1,3-D metabolism are the corresponding epoxides and their direct hydrolysis product 3-chloro-2-hydroxypropanal, respectively." Indeed, data here show that the epoxides (or derivatives thereof) are effective mutagens, and that 3-chloro-2-hydroxypropanal (not tested in this study for mutagenicity) is a significant metabolite of the epoxides in pH 7.4 buffer. This study provides useful mechanistic information, but is not "reviewable" because only summary data were provided. There is no DPR worksheet. Aldous, 4/29/15.

50046-120 162474 Stott, W. T. and H. S. Stewart, "Determination of glutathione transferase activities in several mammalian cell lines", The Dow Chemical Co., Midland, 8/27/96. Laboratory Project Study ID # T2.06-001-014-001. Investigators evaluated activities of glutathione transferase using 4 substrates: racemic ^{14}C-UL-1,3-dichloropropene; 4-chloro-1,3-dinitrobenzene (CDNB); *p*-nitro-phenethylbromide (NPEB); and trans-4-phenyl-3-buten-2-one (TPBO). Sources of GSH transferase activities were rat liver cytosol, mouse liver cytosol, primary rat hepatocytes, CHO cell line, and two Chinese hamster lung cell lines. GSH transferase activities were compared with previously published activities for *Salmonella typhimurium*. GSH transferase activities using ^{14}C-UL-1,3-dichloropropene were about 10-fold higher for the liver 100,000 x g cytosol (rat slightly more active than mouse) compared to preparations from the three cell lines, and over 1000 times higher than was reported for the bacterial cytosol. Aldous, 9/23/99 (no worksheet).

50046-111 161854 Exact duplicate of 50046-120 162474, above.

Creedy, C. L., Brooks, T. M., Dean, B. J., Hutson, D. H., and Wright, A. S. 1984. "The protective action of glutathione on the microbial mutagenicity of the Z- and E-isomers of 1,3-dichloropropene," *Chem Biol Interact* 50:39-48. The Z(cis)- and E(trans)-isomers of 1,3-dichloropropene (DCP) were tested with TA 100 at 10 to 2000 µg/plate, either alone, with rat liver S9, with 5 mM GSH, or with S9 plus GSH. There were robust dose-related increases in revertants with both DCP isomers to the limit of cytotoxicity with DCP alone or with DCP plus S9 in the absence of GSH fortification. The presence of GSH (with or without S9) greatly reduced revertant numbers, although at dose levels of 500 to 2000 µg/plate there was perceptible

response with E-DCP, and more so with Z-DPC. Investigators noted that rat liver cytosol contained somewhat more glutathione than *S. typhimurium* cytosol, and that the percentage of reduced GSH was much higher in the rodent. Also, native activities of GSH transferase activities toward Z-DCP and other GSH substrates were about 100x higher in rat liver than in bacterial cytosol. This is useful supplementary information, but not suitable for DPR review, since only summary data were provided. Aldous, 4/24/15.

Neudecker, T., and Henschler, D. 1986. "Mutagenicity of chloroolefins in the Salmonella/mammalian microsome test. III. Metabolic activation of the allylic chloropropenes allyl chloride, 1,3-dichloropropene, 2,3-dichloro-1-propene, 1,2,3-trichloropropene, 1,1,2,3-tetrachloro-2-propene and hexachloropropene by S9 mix via two different metabolic pathways," *Mutat Res* 170:1-9. Authors investigated metabolism and mutagenicity associated with the above compounds, including the influences of S9, GSH, and particularly of key metabolic inhibitors such as SKF 525 (to inhibit microsomal oxygenases); 1,1,1-trichloropropene-2,3-oxide (TCPO: an inhibitor of epoxide hydrolase); and of cyanamide (CA: an inhibitor of aldehyde dehydrogenase). 1,3-dichloropropene (1,3-DCP) was purified by vacuum distillation, and evidently contained no stabilizer. Key findings with 1,3-DCP led investigators to conclude that the dominant route of metabolism for this compound did not involve epoxide formation, but rather formation of an allyl alcohol, which could subsequently oxidized to a reactive allyl aldehyde, and eventually to the less mutagenic carboxylic acid. Mutagenicity of trans-1,3-DCP was elevated by S9, and this effect was enhanced by addition of CA (evidently by blocking oxidation of the reactive allyl aldehyde). Prolonged incubation of both cis- and trans-1,3-DCP (from 20 min to 120 min) enhanced mutagenicity. Cis- was inherently more mutagenic than trans-1,3-DCP in all cases. In most cases, mutagenicity was roughly proportional to amount of S9 present. Mutagenicity with trans-1,3-DCP was not affected by addition of SKF 525 or TCPO: this was taken to indicate that epoxide formation was not a major feature of 1,3-DCP metabolism. This study contains supplementary information, but provided only summary data, and is not suitable for a DPR worksheet. Also, unlike Schneider et al. (1998, also discussed in this section of the Toxicology Summary), the present study did not assay proposed intermediates. Aldous, 4/30/15.

Neudecker, T., Stefani, A., and Henschler, D. 1977. "In vitro mutagenicity of the soil nematicide 1,3-dichloropropene," *Experientia* 33:1084-1085. The cis- and trans-isomers of 1,3-dichloropropene were tested in the Ames mutagenicity assay system on Salmonella typhimurium tester strain TA 1535. Purity was 99.97% (cis) and 97.46% (trans). Both isomers were clearly mutagenic without S9. Survival was limiting in the range of 0.5 µl/ml top agar. S9 activation rendered test articles slightly less cytotoxic, and elicited fewer revertants (particularly where cytotoxicity was not limiting) than plates without S9. This is a very short publication, and does not require a DPR worksheet. Aldous, 4/29/15.

Mechanistic studies examined by DPR Risk Assessment Group

(Following are principally **abstracts** to published articles which were not assigned to Human Health Assessment Branch Data Review Group for examination. Individual data and quality assurance oversight do not pertain to these data, so that detailed reviews are not possible).

Watson, W. P., Brooks, T. M., Huckle, K. R., Hutson, D. H., Lang, K. L., Smith, R. J., and Wright, A. S. 1987. "Microbial mutagenicity studies with (Z)-1,3-dichloropropene," *Chem Biol*

Interact 61:17-30. This study has confirmed that the direct mutagenicity previously observed when S. typhimurium TA100 was treated with (Z)-1,3-dichloropropene (DCP) was in fact due to trace impurities. These impurities result from autoxidation of (Z)-1,3-DCP and have now been identified. Both (Z)- and (E)-2-chloro-3-(chloromethyl)oxiranes (DCP oxides) were identified as significant products during this autoxidation. The mutagenic impurities formed by autoxidation were completely removed by adsorption chromatography on silicic acid. (Z)-1,3-DCP purified in this way had no direct-acting mutagenicity towards S. typhimurium TA100. However, (Z)-1,3-DCP undergoes mono-oxygenase-catalyzed conversion into bacterial mutagens in the presence of S9 fraction or washed microsomes from rat liver. The glutathione-linked conjugation systems of mammalian tissues provided efficient protection against this indirect mutagenic action. However, the low concentration of glutathione in standard bacterial mutagenicity assays limits the glutathione S-alkyl transferase-catalyzed detoxification of (Z)-1,3-DCP and its primary bioactivation product(s). When the concentration of glutathione was adjusted to the normal physiological concentration, the mono-oxygenase-dependent mutagenic action of (Z)-1,3-DCP was virtually eliminated. These results therefore are consistent with the view that bacterial mutation assays are only qualitative indicators of potential mammalian genotoxicity.

Stolzenberg, S. J., and Hine, C. H. 1979. "Mutagenicity of halogenated and oxygenated three-carbon compounds," *Journal of toxicology and environmental health* 5:1149-1158.
Four structurally related three-carbon compounds, known for their antifertility activity in the male, and the brominated derivatives of two of these compounds were tested for mutagenic activity by the Salmonella typhimurium test of Ames et al. In the presence of strain TA-100, a base-pair substitution detector strain, 1,2-dibromo-3-chloropropane (DBCP), was the most active compound tested but required enzymatic conversion by S9 microsomal preparation to an active mutagen. Three of these compounds containing an epoxide group - epichlorohydrin, epibromohydrin, and glycidol - were highly active direct mutagens, not requiring S9 for activation. α-Chlorohydrin was the least active compound tested; α-bromohydrin was 40 times more active than its chlorinated analog. Epibromohydrin was only slightly more active than epichlorohydrin, but both were highly active. With both of the halogenated epoxides, S9 preparation caused a substantial decrease in mutagenic activity at every concentration tested. All six compounds showed dose-related responsiveness for the base-pair substitution detector strains used. However, they were relatively inactive against the frameshift detector strain of S. typhimurium, TA-98. Glycerol, propylene glycol, and n-propanol, which are also three-carbon compounds containing one or more hydroxy groups, were inactive when tested at high concentrations with strain TA-100.

Talcott, R. E., and King, J. 1984. "Mutagenic impurities in 1,3-dichloropropene preparations," *Journal of the National Cancer Institute* 72:1113-1116.
A widely used pesticide, 1,3-dichloropropene [(DCP) CAS: 542-75-6], has been reported to be mutagenic to Salmonella typhimurium TA100, but large variations in specific mutagenic activity have been observed among different preparations. The purposes of this investigation were to determine the probable cause of the interpreparational variation and to provide new information on the nature of the mutagenic activity. Four preparations were assayed for mutagenic activity before and after silicic acid chromatography. None of the preparations retained mutagenic activity after chromatography, but each contained direct-acting mutagenic polar impurities. The specific mutagenic activities of the unpurified DCP samples appeared to be determined by the

mutagenic activities of their polar impurities. A mixture of mutagenic polar impurities could be regenerated by refluxing a purified DCP preparation for 6 hours. The fraction of polar impurities from one of the preparations was analyzed by gas chromatography-mass spectroscopy. Although its composition was too complex to characterize completely, two known mutagens, epichlorohydrin (CAS: 106-89-8; 1-chloro-2,3-epoxypropane) and 1,3-dichloro-2-propanol (CAS: 96-23-1), were tentatively identified. In view of these results, future studies are required to establish whether DCP itself is a chemical carcinogen or whether its previously observed carcinogenicity resulted from the presence of mutagenic impurities.

Martelli, A., Allavena, A., Ghia, M., Robbiano, L., and Brambilla, G. 1993. "Cytotoxic and genotoxic activity of 1,3-dichloropropene in cultured mammalian cells," *Toxicology and Applied Pharmacology* 120:114-119.
1,3-Dichloropropene (DCP), a widely used soil fumigant previously found to be carcinogenic in both mice and rats, was evaluated for its cytotoxic and genotoxic effects in cultured rodent and human cells. A reduction of cell viability that was dependent on the dose and the length of treatment was observed with the trypan blue and the neutral red assay in both V79 cells and rat hepatocytes exposed to DCP concentrations ranging from 0.18 to 5.6 mM. In the absence of a metabolic activation system, a dose-dependent frequency of DNA single-strand breaks, that were only partially repaired within 24 hr, was revealed by the alkaline elution technique in V79 cells exposed to sub-toxic DCP concentrations. The genotoxicity of DCP was confirmed by the results obtained in metabolically competent primary cultures of both rat and human hepatocytes which displayed similar dose-related amounts of DNA fragmentation and DNA repair synthesis, and showed, in comparison to metabolically deficient V79 cells, a somewhat greater sensitivity to the cytotoxic and DNA damaging effects of DCP. The increase in the frequency of DNA breaks observed in rat hepatocytes after GSH depletion confirms the role of this tripeptide in DCP detoxification; its reduction in hepatocytes simultaneously exposed to metyrapone is consistent with a cytochrome P450-dependent biotransformation of DCP to more toxic metabolites.

Loveday, K. S., Lugo, M. H., Resnick, M. A., Anderson, B. E., and Zeiger, E. 1989. "Chromosome aberration and sister chromatid exchange tests in Chinese hamster ovary cells in vitro: II. Results with 20 chemicals," *Environ Mol Mutagen* 13:60-94.
Twenty chemicals were tested for their ability to induce sister chromatid exchanges (SCEs) and chromosomal aberrations (ABs) in cultured Chinese hamster ovary cells (CHO). These chemicals were tested with and without an added metabolic activation system (rat liver S9 fraction). Four chemicals were negative in both assays, 1 induced ABs only, and 15 were positive for SCEs; 6 of these 15 also induced ABs. The effect of cell harvest time on the ability to detect the induction of chromosomal aberrations was examined for six chemicals. Five of these had caused at least one of the following: cell cycle delay, aberrations observed in first division metaphase cells in the SCE assay, or a weak response in the standard AB assay (10-12-hr growth period). Three chemicals, chlorinated trisodium phosphate, 1,2-dibromo-3-chloropropane, and tetrakis(hydroxymethyl)phosphonium chloride, were positive using both the standard and extended harvest times. N-Nitrosodimethylamine and diphenhydramine HCl were only positive using an extended harvest time, and malonaldehyde was negative using both standard and extended harvest times.

Ghia, M., Robbiano, L., Allavena, A., Martelli, A., and Brambilla, G. 1993. "Genotoxic activity of 1,3-dichloropropene in a battery of in vivo short-term tests," *Toxicology and applied pharmacology* 120:120-125.
The genotoxic activity of 1,3-dichloropropene, which has been classified as possibly carcinogenic to humans, was investigated in rats given high single doses of this chloroolefin. A dose-related amount of DNA fragmentation was observed at doses ranging from 62.5 to 250 mg/kg in liver and gastric mucosa, both of which are targets of DCP carcinogenic activity, as well as in the kidney. The frequency of DNA breaks, that were to a large extent repaired within 24 hr, was higher after po than after ip administration in the liver, while the converse occurred in the kidney. Any evidence of DNA fragmentation was, in contrast, absent in lung, bone marrow, and brain which are not sites of DCP-induced tumor development. A role of cytochrome P450 in the activation of DCP is suggested by the lower degree of liver DNA fragmentation observed in rats pretreated with methoxsalen. DCP produced a dose-dependent reduction of the liver GSH level, an effect that presumably hinders its detoxification and thus favors its DNA-damaging activity. In contrast with the satisfactory prediction of DCP carcinogenic activity provided by the results of the in vivo DNA damage/alkaline elution assay, neither the in vivo rat hepatocyte DNA repair assay nor the micronucleus assay, carried out on bone marrow, spleen, and liver cells of partially hepatectomized rats, supplied any evidence of DCP genotoxicity. NOTE: (Aldous, 6/24/15), in this study, DCP was dissolved in DMSO immediately prior to dosing. Schneider, Quistad, and Casida (1998) had reported that DMSO elicited a spontaneous degradation of DCP toward 2-chloroacrolein, which is not a common metabolite under physiological conditions.

Kevekordes, S., Gebel, T., Pav, K., Edenharder, R., and Dunkelberg, H. 1996. "Genotoxicity of selected pesticides in the mouse bone-marrow micronucleus test and in the sister-chromatid exchange test with human lymphocytes in vitro," *Toxicology letters* 89:35-42.
Selected pesticides (aldicarb, 1,3-dichloropropene, methidathion, parathion, triadimefon, vinclozolin) were tested for their clastogenic and aneugenic activities in the mouse bone-marrow micronucleus (MN) test in vivo and for their sister-chromatid exchange-inducing activities in human lymphocytes in vitro in the presence and absence of an exogenous metabolizing system from rat liver S9. 1,3-Dichloropropene significantly increased the frequencies of micronucleated polychromatic erythrocytes (PCE) in bone-marrow cells of female mice from 3.3 MN/1000 PCE to 15.3 MN/1000 PCE (187 mg per kg body weight). 1,3-Dichloropropene (100 µM) induced 16.0 SCE/metaphase after 24 h of incubation as compared with the basal rate of 11.2 SCE/metaphase (- S9) and of 15.4 SCE/metaphase as compared with 10.5 SCE/metaphase of the control (+ S9). These values were statistically significantly different from each other. The other pesticides tested did neither increase the rate of micronuclei significantly in polychromatic erythrocytes in male nor in female animals. Aldicarb and methidathion induced a significant increase in SCEs in human lymphocytes in vitro only without the metabolic activating system: aldicarb, 5 µM, 24 h incubation: 15.5 SCE/metaphase; control: 12.6 SCE/metaphase; methidathion, 100 µM, 24 h incubation: 15.8 SCE/metaphase, control: 11.1 SCE/metaphase. Parathion, triadimefon and vinclozolin did not have any SCE-inducing effects. NOTE: (by Aldous, 6/24/15), DCP was 95% purity, and was administered in corn oil for in vivo studies. Investigators have no explanation for why females elicited a strong response in vivo and in vitro for micronucleated PCE's, whereas males had no response at all.

Schiffmann D, Eder E, Neudecker T, & Henschler D (1983) "Induction of unscheduled DNA synthesis in Hela cells by allylic compounds," Cancer Lett, 20(3): 263-269. Thirteen allylic compounds, mostly with close structural relationship, were tested for their ability to induce unscheduled DNA synthesis (UDS) in HeLa cells and mutations in the Ames test; 11 induced UDS in dose dependence. Allyl isothiocyanate was negative in UDS (borderline in the Ames test) and acrolein (positive in the Ames test) proved toxic to HeLa cells, therefore UDS measurement was excluded. In general, positive qualitative and quantitative correlation between UDS, Ames test and alkylating properties 9as measured in the 4-nitrobenzyl-pyridine test, NBP) were found. Among structural analogs and typical allylic compounds with various leaving groups, the amount of induced DNA repair at equimolar concentrations decreased in the same order as the mutagenic and alkylating activities in the other 2 test systems: 1,3-dichloropropene (cis) > 1,3-dichloropropene (trans) > 2,3,-dichloro-1-propene; 1-chloro-2-butene > 3-chloro-1-butene > 3-chloro-2-methyl-1-propene > allyl chloride; allyl-methanesulfonate > -iodide > -bromide > -chloride.

von der Hude, W., Scheutwinkel, M., Gramlich, U., Fissler, B., and Basler, A. 1987. "Genotoxicity of three-carbon compounds evaluated in the SCE test in vitro," *Environmental mutagenesis* 9:401-410. Sister chromatid exchange increased with dose of 1,3-dichloropropene, to the limits of cytotoxicity. This study used DMSO as a vehicle. As noted elsewhere in this Summary of Toxicology Data, Schneider, Quistad, and Casida (1998) had reported that DMSO elicited a spontaneous degradation of DCP toward 2-chloroacrolein, which is not a common metabolite under physiological conditions. As a result, this study may not reflect a plausible exposure scenario. No individual data were provided. As there are reviewable reports consistent with the key conclusions already available, this report does not warrant further examination. Aldous, 6/24/15.

Vithayathil, AJ; McClure, C; Myers, JW. (1983) "Salmonella/microsome multiple indicator mutagenicity test," Mutat Res 121(1):33-37. This article primarily seeks to explore the benefits of using a single Salmonella strain (TA98) to address frameshift mutations via histidine backwards mutation as well as rifampicin resistance via a forward base-pair substitution mutation. Several test compounds, including 1,3-dichloropropene, were positive in both respects, suggesting some measure of base-pair and frameshift mutation potential. No individual data were provided. As there are reviewable reports consistent with the key conclusions already available, this report does not warrant further examination. Aldous, 6/24/15.

Stolzenberg, S. J., and Hine, C. H. 1980. "Mutagenicity of 2- and 3-carbon halogenated compounds in the Salmonella/mammalian-microsome test," *Environmental mutagenesis* 2:59-66. This article compared mutagenic potencies of various bromo- and chloro- substituted molecules, including 1,3-dichloropropene, with respect to strain TA-100, with and without S-9. Data for 1,3-dichloropropene demonstrate a mutagenic response, with far more revertants in plates without S-9 at any given dose level. No individual data were provided. As there are reviewable reports consistent with the above observation already available, this report does not warrant further examination. Aldous, 6/24/15.

Haworth, S; Lawlor, TK; Mortelmans, K; et al. (1983) "Salmonella mutagenicity testing for 250 chemicals," Environ Mutagen Suppl 1:3-142. This article codes results from many laboratories

for 250 chemicals as "+" or "-." The entry in the table for 1,3-dichloropropene has a "+" for mutagenicity (not otherwise specified) from a study undertaken by SRI. As there are reviewable reports (positive and negative for mutagenicity) already available, this reference does not warrant further examination. Aldous, 6/24/15.

Registrant interpretive commentary and EPA documents

50046-094 138953 DowElanco reported as FIFRA 6(a)(2) "possible adverse effect" data on 6/20/95 that they had learned that a European 1,3-dichloropropene product (using soybean epoxide as stabilizer, but not a product sold in the United States) elicited stomach lesions considered to be pre-neoplastic in subchronic studies. The memo noted that Sprague-Dawley rats administered 25 mg/kg/day or more daily for 28 days had squamous cell hyperplasia and hyperkeratosis in the forestomach (NOEL = 5 mg/kg/day). Also, CD-1 mice had mild cases of hyperplasia and hyperkeratosis in the forestomach at 200 mg/kg/day after 28 days of treatment (lower doses were included in the study, but not evaluated as of the time of the memo). One of 3 attachments was not otherwise included in the present Summary of Toxicology Data: a Dec. 8, 1989 peer review of Telone II cited several tumor types observed following Telone treatment, including forestomach tumors. One contributing document to that peer review was the May 1985 NTP study employing F344 rats and B6C3F1 mice, both of which acquired forestomach tumors, as noted elsewhere in this Summary. No DPR review, since there were no fundamentally new reviewable data. Aldous, 9/9/99.

50046-007, 932850; Communication to EPA from Dow dated 2/9/82; contains risk assessment based on data from NTP rat and mouse studies (# 036552 & 53) as well as published dermal studies (# 036554), and refers to oncogenic effects noted in the former. (Martz, 8/18/86).

50046-016, 932849, 932853, and 022757; Contain preliminary summary of NTP studies (# 036552 & 53), summary of mutagenicity studies showing positive effects (# 036556-58), and summary of the one generation reproduction study with technical D-D (# 36555), respectively. (Martz, 8/18/86).

50046-016 149370 Brief summaries of toxicology data as of 1982. No reviewable data. Aldous, 3/10/97

50046-139 169270 Rao, K. S., "Telone II: 1,3-dichloropropene (1,3-D): mammalian risk assessment", Final Draft Document submitted to Toxicology Excellence for Risk Assessment (TERA) panel members, Dow AgroSciences, 10/20/98. **Summary makes the following assertions and recommendations**: current production Telone II lacks mutagenic potential under normal physiological conditions. Older formulations had epichlorohydrin as a stabilizing agent, which evidently contributed to mutagenic and oncogenic properties of that material. Current production Telone II lacks epichlorohydrin, and also the associated risks. Dose levels of Telone II high enough to deplete tissue levels of glutathione may elicit oncogenicity (as in rat liver). Often the primary chronic findings are related to local irritant actions of Telone II to mucosal tissues as determined by route (as to the forestomach lining or respiratory tract). Results from exposures to very high dose levels are not representative of plausible human exposures. This assessment concluded that benchmark methodology at the 0.1 level could be used to derive RfC values of 41 $\mu g/m^3$ for chronic toxicity for mouse nasal epithelial effects, or 80 to 800 $\mu g/m^3$ for bronchioalveolar adenomas; and RfD values of 0.022 mg/kg/day for male rat forestomach

hyperplasia and 0.025 to 0.008 mg/kg/day for liver tumors. If cancer potency data are required to be used based on oncogenicity results, the potency calculations would be 1.3 X 10^{-5} $(\mu g/m^3)^{-1}$ and 4.0 X 10^{-2} $(mg/kg/day)^{-1}$, respectively.

The above record continues with attachments, as numbered below:

(1) Several communications dating up to 1993 relating to status of Telone II with the European Community partners.

(2) IRIS record for 1,3-dichloropropene dating to 1993.

(3) U.S. EPA Reregistration Eligibility Document (2 Sept. 1997). This document noted that the negative results in the recent inhalation-route dominant lethal assay (Record No. 162466, above) "... lessen the concern for germ cell [mutagenic] effects; therefore, no further mutagenicity testing is required" (p. 10). The HED derived a Q_1* value of 5.33 x 10^{-2} in 1994 based on male mouse bronchioalveolar adenomas (p. 13). When the HED RfD Peer Review Committee met in January, 1997 to re-evaluate status of Telone II, they determined that there was no need to change the "carcinogenicity classification" nor the Q_1* (p. 14), largely due to positive mutagenicity studies which support the "weight-of-evidence" for Telone II as an oncogen.

(4, 5, 6, and 7) These four attachments provide the mathematical analyses for "point of departure" evaluations. For non-cancer effects, Attachment 4 relates to female mouse nasal epithelial hyperplasia and hypertrophy following inhalation exposure (pp. 55 ff. of report), and Attachment 5 relates to male rat forestomach non-glandular mucosal basal cell hyperplasia (pp. 59 ff. of report). For cancer effects, Attachment 6 relates to inhalation exposure in the mouse oncogenicity study (Record No. 060675), in which male mice had elevated bronchioalveolar adenomas at the highest dose level only. This document proposes a benchmark concentration model (p. 62 of report), however linearized multistage extrapolation analyses are also provided (p. 66 of report). The final cancer evaluation (Attachment 7) relates to male rat liver tumors following oral exposure. Both benchmark and linearized multistage extrapolation analyses were discussed in the report (pp. 68 to 72). Attachments 6 and 7 provided strictly benchmark approach analyses.

Attachments 8 and 9 address dosimetry of inhaled toxicants with respect to respiratory tract anatomy and physiology in order to extrapolate animal data to humans.

The above data do not provide data appropriate for review under SB-950. No worksheet.
Aldous, 7/22/99.

50046-116 162467 DowElanco response to draft HED and EFED RED chapters (relates to 1997 U.S. EPA document on 1,3-dichloropropene). Primary interest for this Summary is the tab: "Response to Tox. Portions - Draft HED RED Chapter". Authors (Stott, W. T. and B. B. Gollapudi) determined that the EPA document made excessive use of outdated studies and applied highly conservative risk extrapolation models. Further, recent mammalian metabolism and mutagenicity studies were often ignored in favor of older *in vitro* studies, hence results often do not have relevance to physiological responses of plausible exposure scenarios. Toxicity studies selected for analyses by U.S. EPA were often bolus-dose treatments, which are known to be able to saturate normal physiological defense mechanisms. Many older studies used obsolete formulations of 1,3-dichloropropene containing up to 2% epichlorohydrin, which is a known mutagenic stabilizing agent not found in current production. Many of the lesions, including tumors, elicited by 1,3-dichloropropene are port-of-entry effects which would not be expected to

occur under most plausible exposure scenarios. No worksheet (no "reviewable" data). Aldous, 7/26/99.

50046-117 162468 This is a continuation of 162467, by the same authors. Primary contribution is evidence that 1,3-dichloropropene does not bind to calf thymus DNA *in vitro* nor in liver nor lungs of F344 rat nor in B6C3F1 mice *in vivo*. Liver GSH depletion was shown at gavage doses of 25 to 100 mg/kg/day for 3 days (NOEL = 12.5 mg/kg/day). Lung GSH was dose-related in the range of 10 to 150 ppm (NOEL not sought nor obtained in this study). See Document No. 50046-119 for details. No worksheet for this brief summary record. Aldous, 7/26/99.

50046-118 162469 Calhoun, L. L. "Additional comments in response to the risk assessment portions of the draft HED RED chapter for 1,3-D: November 21, 1997." This brief record states that threshold-based calculations should be used for chronic and oncogenicity findings. Tables therefore present benchmark dose (BMD) analyses for male rat forestomach basal cell hyperplasia and for male rat hepatocellular adenoma. No worksheet (no "reviewable" data). Aldous, 7/26/99.

Additional abstract(s): studies not subject to GLP oversight, such as journal articles:

Fisher G. D. and Kilgore W. W. "Mercapturic acid excretion by rats following inhalation exposure to 1,3-dichloropropene," Fundam Appl Toxicol. 1988 Aug;11(2):300-7. (Abstract) Rats were exposed to 1,3-dichloropropene (DCP), a commonly used agricultural nematicide, by inhalation to assess the relationship between DCP concentration and the urinary excretion of the mercapturic acid of cis-DCP (3C-NAC). The nose-only exposure system that was used for simultaneously exposing up to four rodents is described. This apparatus provided for generation and monitoring of relative humidity and test vapor concentration. Animals were exposed for 1 hr to concentrations of up to 789 ppm DCP. Urine was collected for 24 hr after exposure. The quantity of 3C-NAC contained in the urine collections exhibited an exposure concentration-dependent increase from 0 to 284 ppm DCP. However, the amount of 3C-NAC was no greater for animals exposed to 398 or 789 ppm DCP than for animals exposed to 284 ppm DCP.