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

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Second Peer Review of Telone II

FROM: Kerry L. Dearfield, Ph.D.
Executive Secretary, Peer Review Committee
Science Analysis and Coordination Branch
Health Effects Division (H7509C)

Kerry L Dearfield 10.30.89

TO: Herman Toma
Product Manager Team #21
Registration Division (H7505C)

The Health Effects Division Peer Review Committee met on 8/23/89 to discuss and evaluate the weight-of-the-evidence on Telone II with particular reference to its carcinogenic potential. From the first Peer Review, Telone II was classified as a Group B_2 - Probable Human Carcinogen based on increased tumors in both sexes of rats and mice after oral administration (tumor types noted included forestomach, liver, mammary, thyroid, adrenal, urinary, and lung tumors). This second Peer Review was convened to assess recently submitted inhalation studies in rats and mice. The Committee reaffirmed the Group B_2 classification with the additional information from the inhalation studies (increased bronchioloalveolar adenomas in male mice). Quantitation was recommended for carcinogenicity risk associated with both the oral route and the inhalation route.

A. Individuals in Attendance:

1. Peer Review Committee: (Signatures indicate concurrence with the peer review unless otherwise stated.)

Reto Engler

Karl Baetcke

John Quest

Esther Rinde

Kerry Dearfield

Lynnard Slaughter

Richard Levy

Marion Copley

William Sette

George Ghali

Julie Du

Robert Beliles

2. Reviewers: (Non-committee members responsible for data presentation; signatures indicate technical accuracy of panel report.)

Alan C. Levy — Alan C. Levy 11-2-89

Yiannakis Ioannou — Y. M. Ioannou 11/9/89

Bernice Fisher — Bernice Fisher 11/2/89

3. Peer Review Members in Absentia: (Committee members who were unable to attend the discussion; signatures indicate concurrence with the overall conclusions of the Committee.)

Penelope A. Fenner-Crisp — Penelope A. Fenner-Crisp

William L. Burnam

Marcia Van Gemert

Richard Hill

4. Other Attendees: Hugh Pettigrew (HED)

B. Material Reviewed:

The Toxicology Branch Peer Review Committee met previously on September 5, 1985 to discuss and evaluate the database on Telone II with particular reference to the carcinogenic potential of the chemical, in particular oral long-term studies in rat and mouse. The Peer Review report for that meeting was reviewed during the current meeting.

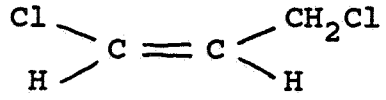
The new and additional material available for review consisted of DER's of more recently performed inhalation carcinogenicity

studies in rat and mouse and other data summaries prepared by Alan Levy; tables and statistical analyses were prepared by Bernice Fisher. The material reviewed is attached to the file copy of this report.

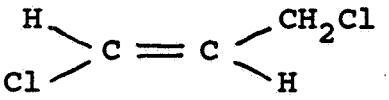
C. Background Information: The active ingredient in Telone II is cis- and trans-1,3-dichloropropene (92-94%). The chemical is produced by Dow Chemical Company and is used as a nematicide/fungicide/insecticide/herbicide. It is applied as a preplant soil fumigant on a variety of agricultural crops. The compound is registered for nonfood agricultural and domestic outdoor use. No tolerances or exemptions for tolerances for residues have been established for food or feed commodities.

The Chemical Abstracts Number (for 1,3-dichloropropene, both isomers) is 542-75-6 and the Tox Chem Number is 324A.

Structure of Telone II active ingredient:



cis-1,3-dichloropropene



trans-1,3-dichloropropene

B

D. Evaluation of Carcinogenicity Evidence for Telone II:

1. National Toxicology Program (NTP) Carcinogenicity Studies

Telone II was orally administered to rats and mice in a chronic bioassay. These studies were the subject of an earlier Peer Review and the full review and references are found in the previous Peer Review Report (from September 5, 1985 meeting; Report dated November 10, 1985).

Briefly, Telone II (mixture of 45% cis- form and 47% trans-form; 2% 1,2-dichloropropane; 1% epichlorohydrin; and 5% chlorinated propenes and hexenes) was administered via gavage in corn oil to groups of 77 Fischer 344 rats/sex/group (52 animals/sex for the main study and 5 animals/sex/group to be killed after 9, 16, 21, 24 and 27 months of dosing) at doses of 0, 25 and 50 mg/kg/exposure. The interim sacrifice information was not discussed at this Peer Review meeting. The same Telone II formulation was administered via gavage in corn oil to 50 B6C3F1 mice/sex/group at doses of 0, 50 and 100 mg/kg/exposure. Rats and mice were exposed for 3 days/week for 104 weeks. The conclusions of the first Peer Review Committee meeting for these two assays are as follows:

"Telone II when administered by gavage at the highest dose level tested (50 mg/kg/day) [sic..this dosing should actually be 50 mg/kg per exposure 3 times a week; this correction applies to the rest of the dosing information in this quote] to rats was associated with significantly elevated incidences of (a) forestomach squamous cell papillomas in males and females, (b) forestomach squamous cell papillomas and carcinomas (combined) in males, and (c) liver neoplastic nodules [sic..the Committee at this 8/23/89 meeting considered these to be adenomas in the absence of any additional information to indicate otherwise] in males. The increased incidence of forestomach tumors was accompanied by a positive trend in the incidence of forestomach basal cell hyperplasia in both male and female rats of both treated groups (25 and 50 mg/kg/day). There were also positive trends for other tumors in rats (i.e., mammary gland adenomas or fibromas in females, thyroid gland follicular cell adenomas or carcinomas in females, and adrenal gland pheochromocytomas in males), but the changes were either not statistically significant and/or did not occur in a dose-related manner."

"Telone II when administered by gavage to mice was associated with elevated incidences of: (a) forestomach squamous cell papillomas in males and females at both dose levels tested (50 and 100 mg/kg/day), (b) forestomach squamous cell papillomas and carcinomas (combined) in females at the highest dose level tested (100 mg/kg/day), (c) urinary bladder transitional cell carcinomas in males at the highest dose level tested and in females at both dose levels tested, (d) lung adenomas in males and females at both dose levels tested (the increase was not strictly dose-related for

males, but was dose-related for females), and (e) lung adenomas and carcinomas (combined) for males at both dose levels tested (the increase was not strictly dose-related). The increased incidence of forestomach tumors was accompanied by an increase in the incidence of stomach epithelial cell hyperplasia in males and females at the highest dose level tested (100 mg/kg/day), and the increased incidence of urinary bladder transitional cell carcinoma was accompanied by a positive trend in the incidence of urinary bladder hyperplasia in both male and female mice of both treated groups (50 and 100 mg/kg/day). .... several deficiencies were present in the mouse study, the primary one being excessive mortality in the control male mice almost one year after the initiation of the study. As a result, the above conclusions pertaining to oncogenicity were based both on concurrent control data, as well as on available historical control data provided by the NTP."

At the same time, the Committee considered the argument that the forestomach tumors produced by Telone II in rats and mice could be attributable to the 1% epichlorohydrin stabilizer used in the test compound. The Committee felt that the carcinogenic response was not entirely due to epichlorohydrin, but due to Telone II.

The Committee at that time classified Telone II as a Group B2 - Probable Human Carcinogen based on increased carcinogenic responses in both sexes of rats and mice. The potency estimate, Q_1^* based on these data in terms of human equivalence is 1.75×10^{-1} $(mg/kg/day)^{-1}$. This calculation was based on the combined tumors [rats with either i) adrenal or thyroid, or ii) forestomach, or iii) liver tumors] from exposed male rats (selected as the most appropriate tumor sites). This potency estimate calculation took into account exposure for only 3 days a week.

2. Mouse Inhalation Carcinogenicity Study

Reference: Stott, W., K. Johnson, L. Calhoun, S. Weiss and L. Frauson. July 13, 1987. Telone II soil fumigant: 2-year inhalation chronic toxicity-oncogenicity study in mice. Unpublished report No. M-003993-009 prepared by Dow Chemical USA. Submitted by Dow Chemical USA, Midland, MI. MRID No. 403123-00 (Reviewed in Document No. 006573).

Telone II (49.5% cis- form, 42.6% trans- form with dichloropropane, 1.8% 1,3-dichloropropane [redacted] was administered to mice via inhalation in live-in chambers. The airflow was approximately 2500 liters/minute (10 air changes/hour). Groups of B6C3F1 mice from Charles River were allotted to 70 animals/sex/group with 10 mice/sex/group to be killed at 6 and 12 month interim sacrifices. Fifty

animals/sex/group were assigned to the 24 month exposure groups. Animals were exposed 6 hours/day, 5 days/week for a total of 510 days of exposure in the 2 year period. Doses used were 0, 5, 20 and 60 ppm. [These doses converted to mg/kg/day based on an average 30 g mouse were approximately 0, 6.88, 27.51, and 82.54 mg/kg/day, respectively. The conversions, rationale and assumptions will be detailed in the quantitative assessment memorandum to be generated.]

In male mice, there was a significant dose-related trend in the occurrence of lung bronchioloalveolar adenomas and a significant difference in the pair-wise comparison of control and the 60 ppm dose group. Additionally, male mice had a significant difference in lacrimal gland cystadenomas in the pair-wise comparison of control and the 20 ppm dose group. In female mice, there was a significant difference in mesenteric lymph node lymphosarcoma in the pair-wise comparison of control and the 5 ppm dose group. Results are reported in Table 1.

a. Discussion of Tumor Data

Telone II was associated with a significant positive dose related trend in lung bronchioloalveolar adenomas (benign tumors) in male mice. A pair-wise comparison at the top dose, 60 ppm, showed a significant increase of bronchioloalveolar adenomas from control (22/60 of animals at risk (37%) versus control of 9/57 of animals at risk (16%)). Historical control data from seven studies indicated a control range of 7-32% for lung bronchioloalveolar adenoma; this included a 20% control incidence from another 2 year inhalation study. The incidence of lung tumors in male mice in this study was outside the historical range. While there were some increases in the incidences of other tumor types (benign lacrimal gland tumors in males and mesenteric lymph node lymphosarcomas in females), these were not considered convincing by the Peer Review Committee to be of great concern. The only agreed upon tumor of concern was the increase in lung tumors in male mice after inhalation exposure. It was noted that female mice in the NTP study also had a dose related increase in lung tumors after an oral exposure (no definitive male data in NTP study due to problems detailed above).

b. Consideration of Adequate Dosing for Assessment of Carcinogenic Potential

In this study, there were no statistically significant effects on mortality on male and female mice after inhalation of Telone II. It was felt there were no compound related effects on clinical signs of toxicological significance, organ weights, clinical

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Table 1. Telone II, Mouse Study - Neoplastic tumor rates[+] and Cochran-Armitage trend test and Fisher's exact test results (p values)

	Dose level (ppm)				Historical
Tumor	0	5	20	60	Data[i]
Male					
Lung Bronchioloalveolar Adenoma	9/57 (16)	6/51 (12)	13/49 (27)	22[a]/60 (37)	(7-32)[ii]
p=	0.001**	0.374	0.132	0.009**	
Lacrimal Gland Cystadenoma	1/57 (2)	6/60 (10)	10/58 (17)	5[b]/60 (8)	(2-16) mean=11
p=	0.301	0.065	0.004**	0.116	
Female					
Mesenteric Lymphnode Lymphosarcoma	3/57 (5)	11[c]/49 (22)	5/47 (11)	6/55 (11)	None Given
p=	0.407	0.010**	0.256	0.227	

[+] Number of tumor bearing animals/number of animals at risk (excluding those that died before 52 weeks)

[i] Historical data - as presented in the report submitted to the OPP by the registrant

[ii] Range from 7 studies including 20% in another 2 year inhalation study

( ) Percent

[a] First lung adenoma observed at week 80

[b] First cystadenoma observed at week 85

[c] First lymphosarcoma observed at week 71

Note: Significance of trend denoted at Control
Significance of pair-wise comparison with control denoted at Dose level

** $p \leq 0.01$ and * $p < 0.05$

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chemistry and hematology. Decreases in body weight gain were considered minimal (3-9% in 60 ppm males and 2-11% in 60 ppm females; although the approximate 10% values at the high end of the range may be approaching adequate decrements). Non-neoplastic histopathology indicated some hyperplasia of the transitional epithelium of the urinary bladder in high dose males and females (lesser effect at 20 ppm), hypertrophy and hyperplasia of respiratory epithelium and degeneration of olfactory epithelium in high dose males and females (considered to be of minimal severity; lesser effect at 20 ppm females), hyperplasia of nonglandular stomach in 60 ppm males only and decreased vacuolation of kidney tubular epithelial cells in high dose males and of liver cells in high dose females. The Peer Review Committee did not consider the body weight gain decrements and non-neoplastic histopathology to be severe enough to suggest that adequately high dosing was attained in this mouse inhalation study. Higher doses could have been utilized for exposure to Telone II vapors. In addition, there was not a subchronic (e.g. 90 day) study to substantiate the choice of the inhalation doses used.

3. Rat Inhalation Carcinogenicity Study

Reference: Lomax, L., L. Calhoun, W. Stott and L. Frauson. July 13, 1987. Telone II soil fumigant: 2-year inhalation chronic toxicity-oncogenicity study in rats. Unpublished report No. M-003993-009R prepared by Dow Chemical USA. Submitted by Dow Chemical USA, Midland, MI. MRID No. 403122-01 (Reviewed in Document No. 006531).

INERT INGREDIENT INFORMATION IS NOT INCLUDED

Telone II (49.5% cis- form, 42.6% trans- form [redacted] was administered to rats via inhalation in live-in chambers. The airflow was approximately 2500 liters/minute (10 air changes/hour). Groups of Fischer 344 rats from Charles River were allotted to 70 animals/sex/group with 10 rats/sex/group to be killed at 6 and 12 month interim sacrifices. Fifty animals/sex/group were assigned to the 24 month exposure groups. Animals were exposed 6 hours/day, 5 days/week (excluding holidays) for a total of 509 days of exposure in the 2 year period. Doses used were 0, 5, 20 and 60 ppm. [These doses converted to mg/kg/day based on an average 400 g rat were approximately 0, 2.68, 10.73, and 32.20 mg/kg/day, respectively. The conversions, rationale and assumptions will be detailed in the quantitative assessment memorandum to be generated on the mouse oncogenicity data discussed above.]

Under the conditions of the study, Telone II did not produce evidence of compound related increased incidences of any tumor types examined. In the gavage study noted above, forestomach

neoplasms were reported. Regarding the current inhalation study, there were no observed neoplasms, one papilloma (control female), 3 instances of focal nonglandular mucosa hyperplasia (one 60 ppm male and two 5 ppm females) and 3 instances of multifocal nonglandular mucosa hyperplasia (two 5 ppm and one 60 ppm females). The Peer Review Committee considered that these non-neoplastic changes in the inhalation study support the carcinogenicity findings in the same target(s) in the oral study.

Consideration of Adequate Dosing for Assessment of Carcinogenic Potential

The Peer Review Committee concurred that there was no evidence of carcinogenicity due to Telone II in this Fischer 344 rat study; however, there was a question whether there was adequately high dosing for assessment of carcinogenic potential in this study. There were no compound related effects on mortality, clinical signs of toxicological significance, organ weights, urinalysis and hematology. Slight (approximately 5% in 60 ppm males and females) decreases in body weight gain were observed during the first year of study, but weights were similar to controls for the remainder of the study. As determined by histopathological examination, the olfactory region of the nasal cavity appeared affected. Animals exposed at the 60 ppm dose (not lower doses) showed decreased thickness of the olfactory epithelium (40% incidence in males, 31% in females) as well as minimal submucosal fibrosis. The Peer Review Committee considered the body weight gain decrements to be minimal and the nasal histopathology not enough to be of real toxicological concern. These minimal signs were not considered to be significant enough for appropriate dose selection to properly assess oncogenic potential. Based on these data, this rat study is considered inadequate. In addition, there was no subchronic (e.g. 90 day) study to substantiate the choice of the inhalation doses used. The interim 6 and 12 month sacrifice data were not included in the 2 year report.

E. Additional Toxicology Data on:

1. Pharmacokinetics, Metabolism, Macromolecular Binding

A pharmacokinetics, metabolism, and macromolecular binding study was performed in male Fischer 344 rats and B6C3F1 mice following a single oral administration of uniformly labeled ^{14}C-cis,trans-1,3-dichloropropene (Document #006546). Targeted dose levels included 1 and 50 mg/kg for rats, pharmacokinetics; 1 and 100 mg/kg for mice, pharmacokinetics; and 1, 50 and 100 mg/kg for rats and mice, macromolecular binding; all delivered in corn oil. In rats, a considerably higher concentration of radioactivity was found in non-glandular stomach, glandular stomach, liver, kidney and bladder than in fat, skin, blood or remaining carcass. In mice, the greatest amount of radioactivity was found in the non-

glandular stomach. Primary routes of excretion in rats and mice were via urine (51-61% rats, 63-79% mice), feces (20% rats, 15% mice) and expiration of $^{14}CO_2$ (15-18% rats, 14% mice) found within 48 hours of exposure. No urinary excretion of unchanged parent compound was observed. Major urinary metabolites found from rats and mice were N-acetyl-S-(3-chloroprop-2-enyl)cysteine (a 1,3-dichloropropene mercapturic acid) and N-acetyl-S-(3-chloroprop-2-enyl)cysteine sulfoxide or sulfone. There was a dose dependent effect of non-protein sulfhydryl depletion found in the non-glandular stomach. The most significant amount of macromolecular binding (to tissue protein) was measured in the non-glandular stomach of both rats and mice.

2. Mutagenicity

A series of acceptable mutagenicity studies have been performed with Telone II and have been submitted to the OPP. These studies indicate that Telone II has mutagenic activity. They minimally satisfy the requirement for the three categories of mutagenicity testing as follows:

Gene mutation assays:

a. Salmonella assay (Document #006546): positive in strains G46, TA100 and TA1535 with and without activation and in strains TA1538 and TA1537 with activation. Responses up to approximately 100X and 10X background in strains TA1535 and TA100, respectively, were obtained.

b. E. coli reverse mutation assay (Document #006546): negative with and without activation up to a toxic concentration of 1000 ug/plate.

c. Chinese hamster ovary (CHO) gene mutation assay (Document #006546): very slight increases (just at 2X background) at unique concentrations were seen induced at the hprt locus. However, no reproducible concentration dependent responses were noted.

Structural chromosomal assays:

a. Mouse micronucleus assay (Document #s 004908, 0005879): male and female CD-1 mice did not have increased micronuclei in exposed bone marrow after single gavage doses of 38, 115 or 380 mg/kg. Some deaths were seen at the top dose and bone marrow was harvested 24 and 48 hours after administration.

Other genotoxic effects:

a. DNA damage in the B. subtilis rec assay (Document #006546): positive for differential killing between DNA repair proficient and DNA repair deficient strains at the one concentration tested, 25 mg/ml.

b. Unscheduled DNA synthesis (UDS) in primary rat hepatocytes (Document #s 004908, 005919, 006546): hepatocytes exposed to concentrations of 1 X 10^{-6} to 3 X 10^{-3} moles/liter did not have induced UDS. Toxicity was observed at $\geq$3 X 10^{-4} moles/liter.

It is clear from these submitted data that Telone II preparations used in these assays were bacterial mutagens. Little evidence for an effect in mammalian cells is found based on these submitted studies.

The National Toxicology Program (NTP) has sponsored many studies which have included 1,3-dichloropropene as one of the test compounds (Tennant et al., Science 236: 933-941, 1987). Briefly, 1,3-dichloropropene is positive in the Salmonella assay $\pm$ activation, the mouse lymphoma assay without activation, and the sister chromatid exchange (SCE) assay in V79 cells $\pm$ activation. It is negative for aberration induction in V79 cells. In another NTP sponsored study (Valencia et al., Environ Mutagen 7: 325-348, 1985), 1,3-dichloropropene induced sex-linked recessive lethal mutations in Drosophila after feeding exposure.

It is clear from these additional data that the tested 1,3-dichloropropene preparations not only produce mutations in bacteria, but also exert effects in mammalian cells in culture. The Drosophila data demonstrate an in vivo effect in an eukaryote as well as effects on germ cells.

3. Developmental and Reproductive Effects

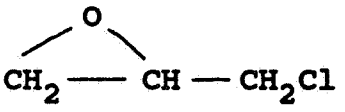
Telone II was assayed for possible reproductive effects in a two-generation inhalation reproduction study with Fischer 344 rats (Document #s 006591 and 006982). Test compound (91.2% minimum) was administered by inhalation (6 hours/day, 5 or 7 days/week) at concentrations of 0, 10, 30 and 90 ppm (air flow was 2500 L/min, air temperature 21-23^{o}C, humidity approximately 50%). The reproductive NOEL was $\geq$90 ppm (HDT). Compound-related effects were noted only at the 90 ppm dose and included stomach lesions, primarily in the non-glandular region, some hyperplasia of the respiratory epithelium and focal degeneration of olfactory tissue. Slight decreases in body weight gain were noted at the HDT with males being more sensitive to this effect. Based on this information, the systemic LEL was determined to be 90 ppm and the systemic NOEL to be 30 ppm.

Two inhalation developmental studies were performed with Telone II in rats and rabbits. These were reviewed in the previous Peer Review report. Maternal toxicity was seen at all dose levels up to and including 120 ppm (HDT) in rats and rabbits with embryo/fetotoxicity seen in rats at 120 ppm. No adverse developmental effects were reported, but there were reporting deficiencies in the reports such that they were classified as supplementary data.

4. Structure-Activity Correlations

Dichloropropene (cis-, trans-1,3-dichloropropene) bears a structural resemblance to several short chain halogenated hydrocarbon compounds that are known carcinogens (e.g. vinyl chloride and epichlorohydrin). Vinyl chloride has been shown to induce lung adenomas and/or adenocarcinoma in rats and mice following inhalation exposure (IARC 7: 291-318, 1974; IARC 19: 377-438, 1979). Similar pulmonary tumors are produced by Telone II in rats and mice. Vinyl chloride has also been shown to induce liver tumors (angiosarcoma) in rats and humans (IARC Suppl 4, 1982). After oral exposure to epichlorohydrin, male rats developed cancers of the forestomach; after inhalation exposure, cancers of the nasal cavity were noted (IARC 11: 131-139, 1976; IARC Suppl 4: 122-124, 1982).

vinyl chloride



epichlorohydrin

F. Weight of Evidence Considerations:

The Committee considered the following facts regarding the toxicology data on Telone II to be of importance in a weight-of-the-evidence determination of carcinogenic potential.

1. Telone II, when administered by oral gavage to Fischer 344 rats at doses of 0, 25 and 50 mg/kg/exposure, 3 days/week, was associated with an increase in i) forestomach squamous cell papillomas in both sexes (HDT) and papillomas and carcinomas combined in males as well as basal cell hyperplasia in both sexes (HDT); ii) liver neoplastic nodules in high dose males; iii) positive trends for other tumor types including mammary gland adenomas or fibromas and thyroid gland follicular cell adenomas or carcinomas in females, and adrenal gland pheochromocytomas in males.

2. Telone II, when administered by oral gavage to B6C3F1 mice at doses of 0, 50 and 100 mg/kg/exposure, 3 days/week, was associated with an increase in i) forestomach squamous cell papillomas in both sexes at both dose levels tested and papillomas and carcinomas combined in females (HDT) as well as epithelial cell hyperplasia in both sexes (HDT); ii) urinary bladder transitional cell carcinomas in males (HDT) and females (both dose levels) as well as positive trend in incidence of urinary bladder hyperplasia in both sexes; iii) lung adenomas in both sexes at both dose levels and lung adenomas and carcinomas combined in males at both dose levels.

3. Telone II, when administered by inhalation to B6C3F1 mice at concentrations of 0, 5, 20 and 60 ppm, was associated with an increase in bronchioloalveolar adenomas in males at the highest dose tested. Hypertrophy and/or hyperplasia of the urinary bladder epithelium, nasal mucosa epithelium and nonglandular stomach were noted. Although tumors of the lung were observed, it was felt based on toxicity parameters that higher dosing could have been utilized in this study.

4. There was no compound related increase in tumors observed in the Fischer 344 rat inhalation study. However, this study was not considered to have been tested adequately at high enough doses to fully assess the carcinogenic potential of Telone II.

5. Although the lung tumors observed in the mouse inhalation study are benign and apparently not life threatening, other factors included: i) a dose-dependent induction of tumors; ii) the incidence was outside the historical control range; and iii) there was site concordance with the oral mouse study. Based on these considerations, the Peer Review Committee concluded that the lung tumors observed in mice after inhalation were biologically significant.

6. Other, non-neoplastic effects observed in the mouse and rat inhalation studies provided evidence for site specific effects by Telone II. There were urinary bladder and nonglandular stomach effects noted and these sites were found to have increased incidences of tumors in the oral studies. These observations provided increased confidence in the compound related induction of tumors seen in the oral studies.

7. It was concluded that, based on available evidence in bacterial, Drosophila and mammalian cell mutagenicity studies, that 1,3-dichloropropene (and hence Telone II) has mutagenic capability.

8. Telone II was not associated with adverse reproductive effects in Fischer 344 rats after inhalation exposure.

9. 1,3-Dichloropropene bears a structural resemblance to several short chain halogenated hydrocarbons that are known oncogens. Vinyl chloride produces lung tumors after inhalation and epichlorohydrin produces forestomach tumors after oral administration and nasal tumors after inhalation.

G. Classification of Carcinogenic Potential:

Criteria contained in the EPA Guidelines [FR51: 33992-34003, 1986] for classifying a carcinogen were considered.

The Peer Review Committee unanimously reaffirmed its previous conclusion that the data available for Telone II provided evidence to classify Telone II as a Group B_2 - Probable Human Carcinogen. This decision was based on i) increased tumors in both sexes of rats and mice after oral administration (tumor types noted included forestomach, liver, mammary, thyroid, adrenal, urinary, and lung tumors), and ii) increased bronchioloalveolar adenomas in male mice after inhalation exposure. Confidence in the compound related induction of tumors was strengthened by the observation of site concordance for neoplastic and non-neoplastic effects seen for the two routes of Telone II administration. Supporting evidence included positive mutagenic activity and a structure activity relationship to several other short chain halogenated hydrocarbons that are oncogenic.

The Committee also decided that quantitation of risk would be appropriate for Telone II. It was further decided that two different quantitation of risk calculations should be performed, one for the oral route and one for the inhalation route. This was suggested based on: i) exposure scenarios for humans may be different based on use, e.g. for applicators, the inhalation exposure may be more relevant than oral exposure; ii) a bolus dose was used in the oral study versus continuous exposure via inhalation - this may affect pharmacokinetics, metabolism, etc.; iii) data are available for both routes of administration from which to calculate risk.

The potency estimate for the oral route has already been derived. The potency estimate, Q_1^*, based on these data in terms of human equivalence is 1.75×10^{-1} $(mg/kg/day)^{-1}$. This calculation was based on the combined tumors [rats with either i) adrenal or thyroid, or ii) forestomach, or iii) liver tumors] from exposed male rats (selected as the most appropriate data). This estimate will be reevaluated to assure consistency with current methodology.

The unit risk for the inhalation route should be based on the increase in bronchioloalveolar adenomas in male mice.