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

Office of Prevention, Pesticides
and Toxic Substances

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SUBJECT: **1,3-Dichloropropene**: Proposed New Use for Drip Irrigation in Vineyards: Revised HED Human Health Risk Assessment; DP Barcode: D347789, PC Code: 029001

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Dow Agrosciences has proposed new uses of 1,3-dichloropropene (1,3-D) for use in established vineyards using drip irrigation. HED prepared a human health risk assessment for the proposed new uses in June 2007 (C. Olinger et.al., 6/6/2007, DP Number D340059). This revision provides additional characterization on the aggregate exposure, bystander exposure, and modifications to the drinking water assessment.

This risk assessment addresses both exposures in the general population and for those occupationally exposed. The key concerns for this assessment were exposures in the general population which occur primarily via inhalation for those in proximity to treated fields and facilities (i.e., bystanders). Dietary exposures from food and water are also addressed.

HED has no concerns that would preclude granting a conditional registration for the proposed use. Confirmatory residue chemistry studies are required before HED can recommend for an unconditional registration as outlined in section 10 of the attached assessment.

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1.0 Executive Summary

The Health Effects Division (HED) of EPA's Office of Pesticide Programs has evaluated the 1,3-dichloropropene (1,3-D) database and conducted a human health risk assessment to support the proposed new uses of 1,3-D in established vineyards.

Use Pattern

1,3-D is a soil fumigant containing an approximately equal mixture of the *cis* and *trans* isomers of the active ingredient. It is registered as a pre-plant control for parasitic root-knot nematodes and other soil pests and diseases for use on vegetables, fruits, nuts, turf, and other field and nursery crops. The registrant has petitioned for a post-plant drip irrigation use in vineyards to control nematodes and *Phylloxera*. 1,3-D would be applied at a rate of 200 ppm via drip irrigation for an effective application rate of approximately 18 lb ai/A up to twice a year, one application during the growing season with a pre-harvest interval (PHI) of 60 days, and a second application after harvest, but no later than three weeks after harvest. The proposed label also states that applications should be made to vineyards that have been established for at least three years.

Hazard Characterization

The toxicology database is considered to be adequate to support of the proposed and existing uses of 1,3-D. 1,3-D showed moderate acute toxicity by the oral and dermal exposure routes (Toxicity was Category II), was moderately irritating to the eye and skin, and was a dermal sensitizer in guinea pigs. It is classified as Toxicity Category IV for acute inhalation toxicity and produced tremors, convulsions, salivation, lacrimation, diarrhea, lethargy and death at concentrations 647 ppm or higher.

Consistent with the irritant properties of 1,3-D, there was evidence of degenerative changes in the nasal olfactory epithelium and histopathological changes of the respiratory epithelium in rats and mice after subchronic inhalation exposure. Following chronic inhalation exposure, the olfactory region of the nasal cavity appeared to be the target organ in rats while lung adenomas were induced in mice. Similarly, following oral exposure, 1,3-D induced histopathological lesions in rats and/or mice including forestomach squamous cell papillomas and carcinomas, liver masses/neoplastic nodules, urinary bladder carcinomas, and alveolar/brochiolar adenomas. Increases in hematopoietic activity and decreased body weights were also noted in dogs and mice, respectively. Accordingly, 1,3-D has been classified as “likely to be carcinogenic to humans” via both the oral and inhalation routes. As a result cancer potency factors (Q_1*) have been calculated for both routes of exposure.

The Food Quality Protection Act (FQPA) requires the Agency to consider special sensitivities of the young to chemical exposure. The 1,3-D risk assessment team has reviewed the entire database for 1,3-D and determined there are no residual uncertainties regarding exposure to children at any developmental stage and recommends that the factor be reduced to 1X.

Dose Response

Based on the toxicity profile and the major exposure routes of 1,3-D, endpoints have been selected for the residential/bystander, occupational, and dietary human health risk assessments. No dermal

endpoints have been selected because of the very low dermal exposure anticipated relative to the high inhalation exposures for this highly volatile chemical.

For inhalation risk assessments, The Agency is currently using the reference concentration (RfC) methodology to derive the human equivalent concentration (HEC) for inhalation exposures in this risk assessment. Under the RfC methodology, endpoint selection is based on the HECs which are derived from the NOAELs of the selected studies. The specific concentrations and endpoints for the exposure scenarios are summarized below:

- **Acute inhalation:** HED selected an **HEC of 75.7 ppm** (non-occupational risk assessment) or **227.0 ppm** (occupational risk assessment) from the **NOAEL of 454 ppm** based on decreased body weight in an acute inhalation toxicity study in rats at the LOAEL of 583 ppm. The selected concentration and endpoint are applicable for a single exposure risk assessment because the rats were treated for 4 hours only. An uncertainty factor (UF) of 30X defines the HED level of concern.

- **Short-term inhalation:** HED selected an **HEC of 5.0 ppm** (non-occupational risk assessment) or **15.0 ppm** (occupational risk assessment) from the **NOAEL of 20 ppm** based on decreased body weight gains in maternal rabbits in the developmental toxicity study. An uncertainty factor (UF) of 30X defines the HED level of concern.

- **Intermediate- term inhalation:** HED selected an **HEC = 0.205 ppm** (non-occupational risk assessment) or **0.86 ppm** (occupational risk assessment) from the NOAEL **of 10 ppm** in the 90-Day Inhalation Toxicity in Rats based on nasal histopathology. An uncertainty factor (UF) of 30X defines the HED level of concern.

- **Long- term inhalation:** HED selected an **HEC = 0.182 ppm** (non-occupational risk assessment) or **0.77 ppm** (occupational risk assessment) from the NOAEL **of 5 ppm** from the Chronic/ Carcinogenicity Study in Mice based on nasal histopathology. An uncertainty factor (UF) of 30X defines the HED level of concern.

- The Integrated Risk Information System's (IRIS) Q_1* of **$4x10^{-6}$ ($\mu g/m^3$)$^{-1}$** [$1.8x10^{-2}$ ppm^{-1}] is based on male mouse lung adenomas in the two-year combined chronic/carcinogenicity inhalation study.

Chronic and cancer endpoints have been selected for the dietary risk assessments. No hazard was identified for acute exposures via the oral route. For the chronic exposures HED based the endpoint on a chronic study in rats where increased decreased body weight and hyperplasia of the stomach was observed at the LOAEL of 12.5 mg/kg/day. The population adjusted dose is based on the NOAEL of 2.5 mg/kg/day and a UF of 100. The 3-chloroacrylic acid (CAAC) and 3-chloroallyl alcohol (CAAL) degradates are assumed to have the same toxicity as the parent. For the cancer assessment, 1,3-D and both degradates were assessed with the parent using the parent's oral Q_1* of $1.22\ x10^{-1}$ $(mg/kg/day)^{-1}$ from the two-year combined chronic/carcinogenicity study based on liver tumors in Fischer 344 rats.

Dietary Exposure

The residues of concern in food and water are the parent compound and the metabolites 3-chloroacrylic acid and 3-chloroallyl alcohol. Adequate analytical methods are available to enforce the tolerances. Thirteen exaggerated rate crop field trials were conducted in support of the proposed new use and generally show non-detectable residues of the parent and metabolites at pre-harvest intervals much shorter than the proposed new uses. Residues at the limit of quantitation (0.003 ppm) for one metabolite were observed in one trial conducted at a seasonal rate approximately five times the proposed rate. A dietary risk analysis was conducted for the combined residues of the parent and metabolites assuming all grapes are treated, residues of all but one analyte at half the limit of detection and the other metabolite at the limit of quantitation. The analysis showed that all populations are exposed to less than 1% of the population adjusted dose (PAD) for chronic risk. This is below the Agency's level of concern (i.e., when dietary exposure exceeds 100% of the PAD). The estimate cancer risk is also below the level of concern.

Residues of concern in drinking water are the *cis* and *trans* isomers of the parent, the 3-chloroacrylic acid (CAAC) and 3-chloroallyl alcohol (CAAL) degradates. The Environmental Fate and Effects Division (EFED) provided the drinking water assessment using simulation models to estimate the potential concentration of 1,3-D and the degradates in surface water while tap water monitoring data were used to estimate concentrations in ground water.

A dietary exposure analysis was conducted for the combined exposure from food and water. The chronic assessment for 1,3-D and the degradates CAAC and CAAC showed that all populations are exposed to less than 1% of the population adjusted dose for food plus water from ground water sources and less than 5% of the population adjusted dose for food plus water from surface water sources. The cancer risk analysis for the combined residues of parent and CAAC and CAAL degradates in food and water from ground water sources did not exceed the level of concern. However, the cancer risk analysis for the combined residues of parent and CAAC and CAAL degradates in food and water from surface water sources based on modeling data exceeded the level of concern. HED considers these estimates to be highly conservative, and actual exposures are likely to be much lower for a number of reasons. First, the models used to estimate the drinking water concentrations are not designed for highly volatile chemicals such as 1,3-D. Rather, PRZM-EXAMS was designed more for chemicals whose main route of dissipation is metabolism in soil and water. When using this type of a model for a chemical whose main route of dissipation is volatilization, the results tend to be overestimates. Moreover, because the existing environmental fate data are insufficient to refine the model estimates, many of the model inputs are likely to be overestimates, thus leading to an overestimation of the surface water concentrations. The limited surface water monitoring data showed that in 123 samples from areas of high use, 1,3-D and its degradates were not detected. Most importantly, however, HED does not expect concentrations of 1,3-D in drinking water from surface water sources to be higher than drinking water from groundwater sources because once introduced into ground water, 1,3-D is shielded from many of the processes that can contribute to its more rapid dissipation from surface water. Accordingly, HED expects that the actual drinking water concentrations for 1,3-D and its degradates from surface water sources to be much lower in drinking water than the model estimates and no more than the concentration in drinking water from ground water sources.

Non-Occupational (Bystander) Exposure

Releases of fumigants, such as 1,3-D, can be categorized in two distinct manners including bystander exposures from single application sites (i.e., treated farm fields) such as area sources (hereon discussed as near field sources) and by ambient air monitoring data where residues could result from many applications within a region (hereon discussed as ambient sources).

Exposures to bystanders from single post-plant agricultural field fumigation events and their associated risks were calculated using the distributional/probabilistic modeling method, as well as the monitoring method. Distributional modeling was done with the PERFUM model. Monitoring method results are based on using monitoring data directly from field volatility studies.

One field volatility study is available to address off-site exposure from this use (MRID 45296101). Using this field volatility study, bystander exposure was modeled using the PERFUM model for the proposed post-plant drip irrigation use on vineyard grapes (see section 6.1 for a summary of results). The data used to assess the post-plant vineyard use is considered to be minimally adequate for modeling purposes. However, the risk estimates for the 1,3-D pre-plant drip agricultural uses (all of which are applied at much higher application rates) are not of concern at 0 meters from treated fields, and the registrant has proposed a 100 ft buffer zone, the Agency expects that the post-plant vineyard use will not pose a risk of concern for bystanders.

Quantitative calculations were completed for acute exposures based on monitoring data and the PERFUM model for a 24 hour duration. However, field volatility studies for 1,3-D indicate that peak emissions from treated fields occur up to 72 hours after application. The monitoring method was used to calculate short-term and cancer risk for all 1,3-D uses and all risk estimates calculated were below the level of concern (LOC) for the proposed post-plant use. At this time, the models cannot readily be used to evaluate exposures for durations longer than 24 hours and the monitoring data are temporally limited.

Risks from ambient air were evaluated using monitoring data from California. These data reflect the existing pre-plant fumigations uses that are applied at rates over 10 times the rate of the proposed post-plant fumigation use. Ambient levels of 1,3-D are not attributable to a specific application event and as such, contributions to the ambient samples may occur from multiple sources. HED has evaluated the available ambient monitoring data for 1,3-D. These data consist of two basic types that include targeted monitoring by the California Air Resources Board (CARB) that occurred in a high use area during the season of use. The other types of data are collected as part of the routine Toxic Air Contaminant (TAC) program and focus on background levels in urban environments.

For the targeted ambient monitoring assessment, none of the risks (acute, short-term, intermediate-term, chronic) exceed HED's level of concern for 1,3-D. Chronic exposure estimates should be considered as rangefinder estimates of exposure because the available monitoring data were not specifically designed for this purpose. Few of the cancer risk estimates exceed HED's level of concern (typically cancer risks greater than 1×10^{-6}). For those locations where risks slightly exceeded the level, monitoring in the following year showed risks well below the level of concern, so there is no concern over a lifetime of exposure. Also, since sampling was done in the high use season, air concentrations used for the cancer risk assessment are not expected to be of concern for exposures which could occur throughout the year.

HED also considered exposure resulting from urban background air concentrations. None of the estimated risks (acute, short-term, intermediate-term, chronic, or cancer) exceed HED's levels of concern. Because of the large number of non-detectable residues observed in these monitoring data, a chronic risk assessment is probably less germane than a short- or intermediate-term assessment for 1,3-D. However, chronic exposure to urban background ambient air incorporating non-detectable (ND) residues as ½ LOD is assessed as a upper bound of exposure and is assumed to present a conservative assessment of risk.

Aggregate Exposure Assessment

When there are potential residential exposures to a pesticide, the Food Quality Protection Act (FQPA) requires consideration of the aggregate exposures from three major pathways: oral, dermal and inhalation exposures provided there is common toxicity among the various routes. Although 1,3-D is not used in residential settings, due to the volatility of 1,3-D residential exposure may occur when 1,3-D is applied to fields near residential areas. Accordingly, the only residential exposures will be inhalation exposures. Dietary exposure may occur from food from the proposed new use on grapes and from water as a result of the proposed new use and the existing pre-plant fumigations.

For the acute, short-, intermediate-, and long-term assessments the toxicity endpoints selected for inhalation and dietary exposures should not be aggregated as there is not a common toxicity observed. 1,3-D has been classified as likely to be carcinogenic to humans via the oral and inhalation routes. However, the types of tumors observed in the inhalation and oral studies were different. Therefore, the oral and inhalation exposures should not be aggregated. The aggregate exposure from food and water sources is discussed in the *Dietary Exposure* section of this summary.

Occupational Exposure

Mixer/Loader/Applicator Exposure

HED has no new data for worker exposure resulting specifically from the post-plant drip irrigation application of 1,3-D. However, mixing and loading techniques for the proposed use are expected to be similar to loading techniques assessed for the existing agricultural uses of 1,3-D. The exposure for these loading methods was assessed in the most recent Reregistration Eligibility Document (RED). Specifically, air concentration levels from 1,3-D-specific worker exposure monitoring studies were used to estimate occupational exposure for workers using bulk/mini-bulk loading. The occupational assessment presents risk with and without the use of OV respirators. However, mitigation on current 1,3-D labels requires the use of half-face respirators with either an organic-vapor-removing cartridge with a prefilter approved for pesticides or a canister approved for pesticides (also referred to as OV respirators) for all occupational workers before and during a 5 day REI. The use of OV respirators, which decreases exposure levels by a factor of at least 10, and adequately addresses occupational risk. It should be noted that the study data used to estimate bulk and mini-bulk loader exposure are based on a much higher application rate than the proposed application rate for the post-plant vineyard use. For this reason, loader exposure for the proposed post-plant use is expected to be significantly lower than that assessed for bulk and mini-bulk loading for the existing pre-plant uses of 1,3-D.

Since 1,3-D is formulated as a liquid there is some potential for dermal and eye contact. The use of mitigation controls such as personal protective equipment (PPE) and closed transfer systems

minimizes the potential but does not eliminate it. However, the high vapor pressure of 1,3-D makes quantifying any potential low level dermal exposures very difficult. Although 1,3-D may be irritating to the skin and eyes, no dermal endpoints of concern were selected for risk assessment purposes. Since realistic quantification of dermal risk is not possible, PPE for dermal protection should be based on the acute toxicity of the end-use product as described in the Worker Protection Standard and mitigation measures for dermal exposure (i.e. PR Notice 93-7, 1995 label amendments, 9/30/98 agreement with Dow).

Post-application Exposure

One field volatility study is available to address off-site exposure from this use (MRID 45296101). Using this field volatility study, acute occupational post-application exposure is modeled using the PERFUM model for the proposed post-plant drip irrigation use on vineyard grapes (see section 6.1 for a summary of results).

Environmental Justice Considerations

Potential areas of environmental justice concerns, to the extent possible, were considered in this human health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations," http://www.epa.gov/compliance/resources/policies/ej/exec_order_12898.pdf.

As a part of every pesticide risk assessment, OPP considers a large variety of consumer subgroups according to well-established procedures. In line with OPP policy, HED estimates risks to population subgroups from pesticide exposures that are based on patterns of that subgroup's food and water consumption, and activities in and around the home that involve pesticide use in a residential setting. Extensive data on food consumption patterns are compiled by the USDA under the Continuing Survey of Food Intake by Individuals (CSFII) and are used in pesticide risk assessments for all registered food uses of a pesticide. These data are analyzed and categorized by subgroups based on age, season of the year, ethnic group, and region of the country. Additionally, OPP is able to assess dietary exposure to smaller, specialized subgroups and exposure assessments are performed when conditions or circumstances warrant. Whenever appropriate, non-dietary exposures based on home use of pesticide products and associated risks for adult applicators and for toddlers, youths, and adults entering or playing on treated areas postapplication are evaluated. Further considerations are currently in development as OPP has committed resources and expertise to the development of specialized software and models that consider exposure to bystanders and farm workers as well as lifestyle and traditional dietary patterns among specific subgroups. This assessment specifically addresses exposure to bystanders and those living near fields that may be treated with 1,3-dichloropropene.

Review of Human Research

This risk assessment does not rely on any data from studies in which human subjects were intentionally exposed to a pesticide or other chemical.

Regulatory Recommendations

The registrant should submit a revised Section F proposing tolerances for the combined residues of *cis*-1,3-dichloropropene, *trans*-1,3-dichloropropene *cis*-3-chloroacrylic acid, *trans*- 3-chloroacrylic acid, *cis*-3-chloroallyl alcohol , and *trans*-3-chloroallyl alcohol at 0.018 ppm. Pending submission of a revised Section F there are no residue chemistry issues that would preclude granting a conditional registration on grapes, or establishment of tolerances for the combined residues of *cis*-1,3-dichloropropene, *trans*-1,3-dichloropropene *cis*-3-chloroacrylic acid, *trans*-3-chloroacrylic acid, *cis*-3-chloroallyl alcohol, and *trans*-3-chloroallyl alcohol, as follows:

Grapes ..... 0.018 ppm

HED recommends that conversion of a conditional registration to an unconditional registration may be considered upon submission of the following confirmatory analytical method, storage stability, and field volatility studies described below.

860.1340 Residue Analytical Methods
An independent laboratory validation is required for the tolerance enforcement method that determines the 3-chloroacrylic acid and 3-chloroallyl alcohol metabolites.

OPPTS Guideline 860.1360 Multiresidue Methods
Multiresidue method data are required for 1,3-dichloropropene and its 3-chloroacrylic acid and 3-chloroallyl alcohol metabolites.

OPPTS Guideline 860.1380 Storage Stability
A storage stability study demonstrating stability of 1,3-dichloropropene and its 3-chloroacrylic acid and 3-chloroallyl alcohol metabolites in grapes for at least 154 days is required.

2.0 Ingredient Profile

1,3-dichloropropene (1,3-D) is currently registered for use as a soil fumigant on numerous field and nursery crops. 1,3-D products are liquid formulations containing 63.5 to 97.5% of the active ingredient 1,3-D. 1,3-D is a mixture of the cis and trans isomers, with approximately equal quantities of the two isomers.

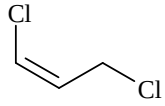
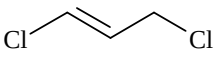
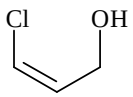
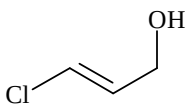
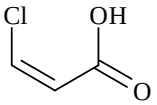
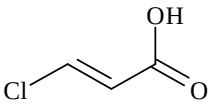
The registered products may be applied by drip irrigation (Telone EC), and row and broadcast applications (Telone II, Telone, C-17, Telone C-35, Telone C-15). Several 1,3-D products (Telone C-17 and Telone C-35) also contain the fumigant chloropicrin (trichloronitromethane).

Broadcast applications of 1,3-D for control of nematodes and garden symphylans[1] are made at rates up to 259 lbs ai/A for vegetables up to 202 lbs ai/A for field crops and up to 366 lbs ai/A for fruit and nut crops. These are the highest label applications rates available for agricultural use of 1,3-D.

The Agency has issued registrations for 1,3-D on golf courses. The end-use product, Curfew® is a liquid formulation. Curfew® is injected into turf 5 inches deep, at a rate of 5 gallons per acre.

In addition to the agricultural and golf course fumigation uses, the registrant requested a turf farm use. In this document, the turf farm use was not assessed. HED asked that the registrant submit additional label language to clarify the turf farm use patterns. To date, HED has not received a revised label from the registrant.

2.1 Structure and Nomenclature

Table 2.1. Test Compound Nomenclature		
Compound Structure		
Common name	cis-1,3-Dichloropropene	trans-1,3-Dichloropropene
Company experimental name	1,3-D	
IUPAC name	(EZ)-1,3-Dichloropropene	
CAS name	1,3-Dichloro-1-propene	
CAS registry number	542-75-6	
End-use product (EP)	Cordon™, Telone™	
Compound Structure		
Common name	cis-CAAL	trans-CAAL
IUPAC name	(EZ)-3-chloroprop-2-en-1-ol	
CAS registry number	4643-05-4	4643-06-5
Compound Structure		

[1]Symphylans are small, many -legged soil dwelling arthropods.

Table 2.1. Test Compound Nomenclature		
Common name	cis-CAAC	trans-CAAC
IUPAC name	(EZ)-3-chloroacrylic acid	
CAS name	1609-93-4	2345-61-1

2.2 Physical and Chemical Properties

Table 2.2. Physicochemical Properties of the Technical Grade Test Compound 1,3-Dichloropropene.		
Parameter	Value	Reference
Boiling point	104 °C for cis isomer; 112.6 °C for trans isomer	1,3-Dichloropropene Reregistration Eligibility Decision Document (12/1998)
pH	Not available	
Density	1.209 g/mL at 25 °C	1,3-Dichloropropene Reregistration Eligibility Decision Document (12/1998)
Water solubility	2,180 mg/L for cis isomer; 2,320 mg/L for trans isomer	
Solvent solubility	Not available	
Vapor pressure	34.3 mm Hg for cis isomer at 25 °C; 23.0 mm Hg for trans isomer at 25 °C	1,3-Dichloropropene Reregistration Eligibility Decision Document (12/1998)
Dissociation constant, pK_a	Not available	
Octanol/water partition coefficient, $Log(K_{OW})$	Not available	
UV/visible absorption spectrum	Not available	

2.3 Proposed New Use Directions

The registrant is proposing a new uses to suppress nematodes and grape *Phylloxera* in established vineyards using drip irrigation. The most recent revision to the label, dated 12/18/07, includes a 100 foot buffer zone between the edge of the field and occupied structures.

Table 2.3. Summary of Directions for Proposed New Use of 1,3-Dichloropropene						
Applic. Timing, Type, and Equip.	Formulation [EPA Reg. No.]	Applic. Rate (lb ai/A)	Max. No. Applic. per Season	Max. Seasonal Applic. Rate (lb ai/A)	PHI (days)	Use Directions and Limitations
Grapes						
Drip irrigation	Cordon® [62719-GAG]	17.7	2	35.4	60	Only one application may be made during the growing season; another application may be made within three weeks after the fruit is harvested. Product should not be applied to vines planted within the previous three years.

The application rates were calculated using product density and other information. The label specifies the drip irrigation solution should have a maximum concentration of 200 ppm, and that no more than 4 gallons of the Cordon product may be used per acre per year.

3.0 Hazard Characterization/Assessment

3.1 Hazard Characterization

3.1.1 Database Summary

Studies Available and Acceptable (animal, human, and general literature) Acceptable studies are available *via* both the inhalation and oral route including: 1) acute inhalation study; 2) inhalation developmental toxicity studies in rats and rabbits, 3) subchronic inhalation toxicity studies in rats and mice; 4) chronic toxicity/carcinogenicity studies via both oral and inhalation routes in rats, mice and dogs; and 5) inhalation multigeneration reproductive toxicity study.

Metabolism, toxicokinetic, mode of action data
A guideline oral metabolism study in rats and a pharmacokinetic study have been conducted in the rat and the mouse. These studies indicate that 1,3-D is rapidly absorbed and distributed. There was rapid elimination in the urine and as CO_2 in expired air and small amounts in the feces. Nine metabolites were isolated from urine with two being identified as 1,3-DCP-mercapturic acid and the sulfoxide derivative.

The registrant has proposed that 1,3-D exposure may lead to lung and liver tumorigenesis through a mode of action (MOA) other than mutagenicity. In two mechanistic studies submitted to the HED, the registrant has proposed that 1,3-D exerts its tumorigenic effects by acting as an initiator and/or promoter. However, the data from these studies was insufficient to fully support this proposed MOA. Given the evidence of mutagenicity (gene mutations in bacteria and cultured mammalian cells in conjunction with clastogenic activity and sister chromatid exchanges in several mammalian cell lines and induction of DNA strand breaks both *in vitro* and *in vivo*) seen in the 1,3-D data base, mutagenicity is considered a plausible MOA. As a result of these observations, the HED has concluded that 1,3-D should remain classified as **likely to be carcinogenic to humans** using the linear approach (Q_1*) for quantification of risk.

Sufficiency of studies/data

The currently available toxicological database for 1,3-D is adequate for selecting endpoints for risk assessment purposes.

3.1.2 Toxicological Effects

1,3-D showed moderate acute toxicity by the oral and dermal exposure routes (Toxicity was Category II), was moderately irritating to the eye and skin, and was a dermal sensitizer in guinea pigs. It is classified as Toxicity Category IV for acute inhalation toxicity and produced tremors, convulsions, salivation, lacrimation, diarrhea, lethargy and death at concentrations 647 ppm or higher. Historically, OPP has classified agricultural pesticides into four acute toxicity categories ranging from Toxicity Category I (extremely toxic) to Toxicity Category IV (minimally toxic). These toxicity categories reflect the doses or concentrations that are lethal to 50% of the test animals in the group or severely irritating. Acute toxicity studies, however, seldom evaluate other endpoints such as histopathology or clinical chemistry. As a result, a compound classified as Category IV may nevertheless be acutely toxic even in the absence of mortality by eliciting effects ranging from slight

changes in clinical chemistry or portal of entry effects to severe effects such as convulsions, ataxia, tissue necrosis, etc.

The major routes of exposure to 1,3-D are the inhalation and oral (food and drinking water) routes.

The pattern of toxicity attributed to 1,3-D exposure *via* the inhalation route includes histopathology findings in the nasal cavity (e.g., degeneration of the olfactory epithelium) and non-glandular stomach, as well as generalized systemic toxic effects (body weight, body weight gain, and food consumption decrements). In addition, 1,3-D chronic inhalation exposure resulted in an increased incidence of bronchioloalveolar adenomas. Based on this finding, 1,3-D has been classified as "likely to be carcinogenic to humans" via the inhalation route. The cancer potency factor for humans was calculated by IRIS to be 4×10^{-6} $(\mu g/m^3)^{-1}$.

Oral exposure to 1,3-D led to an increase in histopathological findings of the non-glandular stomach, increased liver weights, mycrocytic anemia, increased hematopoiotic activity, and decreases in body weight and body weight gain. After chronic oral exposure, 1,3-D caused increases in the incidences of basal cell hyperplasia in the non-glandular stomach, squamous cell papillomas and carcinomas of the forestomach, and neoplastic nodules in the liver. Based on these findings, 1,3-D has been classified as "likely to be carcinogenic to humans" via the oral route.

Several mutagenicity studies with 1,3-D show that this compound acts as a genotoxic agent consistent with the carcinogenicity pattern seen throughout the database by both oral and inhalation routes.

In addition to the parent compound (1,3-D), two degradates were identified, 3- chloroallyl alcohol and 3- chloroacrylic acid. These degradates are assumed to have toxicity equal to the parent compound. Consequently, the risk assessment for the parent compound will be protective of the potential toxic effects elicited by the two degradates.

3.2 Absorption, Distribution, Metabolism, Excretion (ADME)

Pharmacokinetics studies were conducted in Fischer 344 rats and B6C3F1 mice *via* the oral route. The primary route of excretion for both species was the urine. Following oral administration, most of the radiolabel was found in the stomach and gastrointestinal tract with lesser amounts in the kidneys, liver, urinary bladder, skin, fat, blood and carcass. Oral administration also depleted the non-protein-sulfhydryl contents of several tissues including the non-glandular stomach (both time- and dose-dependent). Dose-related increases in macromolecular bindings were noted in several organs with the highest binding sites being found in the non-glandular stomach. The two major urinary metabolites were identified as 1,3-DCP-mercapturic acid and its sulfoxide (or sulfone) derivative.

In another study with Fischer 344 rats, gavage administration of 1,3-D for 14 days resulted in rapid absorption from the gastrointestinal tract with distribution to all tissues examined. Highest concentrations appeared in the non-glandular stomach and urinary bladder. There was rapid elimination in the urine, as carbon dioxide in expired air and small amounts in the feces. Nine metabolites were isolated from urine with two being identified as 1,3-D-mercapturic acid and the sulfoxide derivative. No parent compound was present in the urine.

3.3 FQPA Considerations

3.3.1 Adequacy of the Toxicity Database

The database is adequate to characterize potential pre- and/or post-natal risk for infants and children. Acceptable/guideline studies for developmental toxicity studies in rats and rabbits, and a reproduction study in rats were available for FQPA assessment. A summary of the toxicity studies that have been submitted for 1,3-D may be found in Appendix A to this document.

3.3.2 Evidence of Neurotoxicity

There was no evidence of neurotoxicity observed in the toxicology database. Although specific neurotoxicity studies have not been submitted, there are no indications of neurotoxicity in any of the acute, subchronic, and toxicity studies.

3.3.3 Developmental Toxicity Studies

Rabbit and rat inhalation developmental toxicity studies have submitted. Developmental toxicity was not observed in either study at any dose, but maternal toxicity was observed at all doses in the rat study, and at the mid- and high-doses in the rabbit study.

Although oral developmental toxicity studies have not been submitted, HED considers the inhalation developmental studies to be sufficient. The inhalation studies are likely to overestimate the internal dose that would result from an oral exposure given that chemicals will enter the circulation before many of the detoxification processes associated with oral exposure (e.g. first pass effect) occur. Moreover, chemicals in the respiratory tract enter the blood stream more readily than chemicals in the gastrointestinal tract (GI) since only ~ 2μM separate the chemical in the alveolar space of the lung and the blood stream while several cellular layers separate the chemicals in the lumen of the GI tract from the blood stream.

3.3.4 Reproductive Toxicity Study

An inhalation rat reproduction study has been submitted and is discussed in Appendix A. Although local and systemic effects were observed in the parent, no effects were observed in the offspring, and no effects on reproduction were observed.

3.3.5 Additional Information from Literature Sources

A literature search did not reveal additional information that would impact the risk assessment.

3.3.6 Pre-and/or Postnatal Toxicity

3.3.6.1 Determination of Susceptibility

There is no concern for increased quantitative and/or qualitative susceptibility after *in utero* or postnatal exposure to 1,3-dichloropropene in developmental toxicity studies in rats and rabbits, or a reproduction study in rats.

3.3.6.2 Degree of Concern Analysis and Residual Uncertainties for Pre- and/or Postnatal Susceptibility

The purposes of the Degree of Concern analysis are: (1) to determine the level of concern for the effects observed when considered in the context of all available toxicity data; and (2) to identify any residual uncertainties after establishing toxicity endpoints and traditional uncertainty factors to be used in the risk assessment. If residual uncertainties are identified, then HED determines whether these residual uncertainties can be addressed by a FQPA safety factor and, if so, the size of the factor needed.

There is no evidence (quantitative or qualitative) of increased susceptibility and no residual uncertainties with regard to pre- and/or postnatal toxicity following *in utero* exposure to rats or rabbits and pre and/or post-natal exposures to rats. Therefore, it is recommended that the FQPA safety factor be reduced to 1X and no additional safety factors are needed (section 3.4).

3.3.7 Recommendation for a Developmental Neurotoxicity Study

There was no evidence of neurotoxicity observed following acute, subchronic, or chronic exposure to 1,3-dichloropropene, and no clinical signs of neurotoxicity were observed following pre-natal or postnatal exposure; therefore, a developmental neurotoxicity study is not warranted at this time.

3.4 FQPA Safety Factor for Infants and Children

Based on the hazard and exposure data, the 1,3-dichloropropene risk assessment team has recommended that the FQPA Safety Factor be reduced to 1X. There is a complete toxicity database for 1,3-dichloropropene and exposure data are complete or are estimated based on data that reasonably account for potential exposures. There is no evidence of susceptibility following *in utero* and/or postnatal exposure in the developmental inhalation toxicity studies in rats or rabbits, and in the 2-generation inhalation rat reproduction study. There are no residual uncertainties concerning pre- and post-natal toxicity and no neurotoxicity concerns. The chronic and cancer dietary food exposure assessments assume 100% crop treated for grapes, the commodity of interest. The drinking water exposure assessment is based on conservative models and monitoring data. The residential exposure assessment is not likely to underestimate bystander exposure. Based on these data and conclusions, the FQPA Safety Factor can be reduced to 1X.

3.5 Hazard Identification and Toxicity Endpoint Selection

The primary exposure pathways for 1,3-D are *via* inhalation, food, and drinking water. Exposures via the inhalation route may be acute (less than 24 hours), short-term (1-30 days), or intermediate-term (1 month- 6 months) in duration. At this time the Agency does not anticipate long-term (> 6 months) exposures. Exposure *via* food and drinking water may; however, be long-term (> 6 months).

3.5.1 Acute Reference Dose (aRfD) - Females age 13-49

No appropriate endpoint attributable to a single exposure (dose) was identified from oral toxicity studies for females 13+.

3.5.2 Acute Reference Dose (aRfD) - General Population

No appropriate endpoint attributable to a single exposure (dose) was identified from oral toxicity studies for the general population.

3.5.3 Chronic Reference Dose (cRfD)

Study Selected**:** Combined Chronic Toxicity/Carcinogenicity (B6C3F1 mice)
MRID No.**:** 43757901
Executive Summary: See Appendix A, Guideline § 870.3700.
Dose and Endpoint for Risk Assessment: NOAEL = 2.5 mg/kg/day based on lower body weights and decreased body weight gain (both sexes) seen at a LOAEL = 12.5 mg/kg/day.
Uncertainty Factor(s): 100X [10 interspecies; 10X intraspecies]
Comments about Study/Endpoint/Uncertainty Factors: The route and duration of exposure are appropriate for selection of the chronic dietary endpoint.

3.5.4 Incidental Oral Exposure (Short- and Intermediate-Term)

1,3-Dichloropropene is not used in residential settings, so incidental oral exposures are not expected. Also the volatile nature of 1,3-D reduces the potential for significant residues of 1,3-D and its degradates in the upper layer of soil that may be consumed by young children.

3.5.5 Dermal Absorption

Dermal absorption data have not been submitted for 1,3-dichloropropene.

3.5.6 Dermal Exposure (Short-, Intermediate- and Long-Term)

Dermal toxicity studies have not been submitted for 1,3-D. Since 1,3-D is formulated as a liquid there is some potential for dermal and eye contact. The use of mitigation controls such as personal protective equipment (PPE) and closed transfer systems minimizes the potential but does not eliminate it. However, the high vapor pressure of 1,3-D makes quantifying any potential low level dermal exposures very difficult. Although 1,3-D may be irritating to the skin and eyes, no dermal endpoints of concern were selected for risk assessment purposes. Since realistic quantification of dermal risk is not possible, PPE for dermal protection should be based on the acute toxicity of the end-use product as described in the Worker Protection Standard and mitigation measures for dermal exposure (i.e. PR Notice 93-7, 1995 label amendments, 9/30/98 agreement with Dow).

3.5.7 Inhalation Exposure (Acute, Short-, Intermediate- and Long-Term)

The critical effects of 1,3-D exposure *via* the inhalation route are decreased body weight for acute exposures, and histopathological lesions in the olfactory region of the nasal cavity for longer term exposures. In this risk assessment, endpoint selection will be based on the endpoints occurring at the lowest HECs (which may or may not be the lowest animal NOAEL) derived using the RfC methodology. In this methodology, different HECs may be calculated for the same experimental NOAEL due to: 1) the different algorithms used to derive HECs for systemic *versus* portal of entry effects; or 2) the time adjustments conducted for non-occupational *versus* occupational exposure scenarios. The differences between systemic *versus* portal of entry effects, arise from the use of

different calculations to estimate the inhalation risk to humans which are dependent on the regional gas dose ratio (RGDR). In the case of systemic *versus* portal of entry effects, different RGDRs are derived for each type of toxicity. For non-occupational *versus* occupational exposure, the differences arise because while it is presumed that non-occupational exposure may occur 24 hours/day, 7 days/week; occupational exposure occurs only during the course of an average workweek (8 hours/day and 5 days/week). For further details on the critical studies used for endpoint selection and the 1,3-D toxicity profile the reader is referred to Appendix A. For additional information on the methodologies used in this risk assessment and the HEC arrays, please refer to Appendix B. The toxicity endpoints selected for risk assessment are presented below.

3.5.7.1 Acute Inhalation Exposure

For the acute inhalation scenario, two acute inhalation rat studies were selected for establishing the toxicity endpoints for risk assessment. A brief synopsis of the studies and rationale for their use is provided below:

Executive Summaries: In one acute inhalation study (MRID No. 40220903), Wistar rats were exposed to Telone II at 454, 647, 699, 762, 832 or 958 ppm for 4 hours (whole body exposure). In a second study (MRID 41672201), Fischer 344 rats were exposed to cis- 1, 3 dichloropropene at 0, 583, 771, or 1020 ppm for 4 hours (whole body exposure). **The NOAEL = 454 ppm based on decreased body weights at the LOAEL of 583 ppm.**

Dose and Endpoint for Risk Assessment: HECs = 75.67 ppm (non-occupational risk assessment) or 227.0 ppm (occupational risk assessment)**.** Though body weight changes are not customarily considered acute effects, the body weight decreases observed at doses ≥ 583 ppm were the outcome of a single exposure to 1,3-D during the acute inhalation toxicity study. These decreases were first manifested on day 2 of the study (one day after cessation of exposure) and persisted for 7 days. Consequently, the duration of exposure in the studies is appropriate for this risk assessment. The exposure concentration selected for this risk assessment will be protective of the marginally decreased body weight seen during days 2 through 7 at 583 ppm and the clinical signs and mortality seen at ≥647 ppm. An UF of 30X defines HED's level of concern in accordance with guidance provided in the RfC methodology.

3.5.7.2 Short-term Inhalation Exposure

The short-term inhalation risk assessment was based on the findings from the following subchronic inhalation studies:

Study Selected: Developmental Toxicology (Inhalation) in Rabbits

Executive Summary (2 weeks): In a developmental toxicity study (MRID 001444715 and 00152848), New Zealand rabbits (17-24 females/group) were exposed to concentrations of 1,3-D (90.1%) at 0, 20, 60 or 120 ppm (equivalent to approximately 0, 0.091, 0.272 or 0.545 mg/L) 6 hours/day during gestation days 6 through 18. **The maternal NOAEL was 20 ppm (0.091 mg/L). The maternal LOAEL was 60 ppm (0.272 mg/L) based on decreased body weight gains compared with controls.** The developmental NOAEL was 120 ppm (0.545 mg/L). The developmental LOAEL was >120 ppm (> 0.545 mg/L, HDT).

Dose and Endpoint for Risk Assessment: HEC = 5.0 ppm (non-occupational exposure) or 15.0 ppm (occupational exposure) based on decreased body weight gains. Although a lower HEC was identified in the dominant lethal study assay (HEC =2.5 or 7.5 ppm for non-occupational and occupational risk assessments, respectively), the HEC from the developmental toxicity study in rabbits was used. The lower HECs identified in the dominant lethal assay appear to be an artifact of dose selection/dose spread since clear NOAELs were identified at 30 ppm (HEC = 5.3 or 22.5 ppm for non-occupational and occupational exposure, respectively) in 30-day inhalation toxicity studies in rats and mice. Thus the Agency has concluded that use of the HECs from the developmental toxicity study in rabbits would be protective of the decreased body weights seen at 60 ppm (HEC = 15 or 45 ppm for non-occupational and occupational exposure, respectively) in the dominant lethal assay. An UF of 30x defines HED's level of concern.

3.5.7.3 Intermediate-term Inhalation Exposure

13-Week Inhalation Toxicity in Rats; OPPTS 870.3100 [§84-4]

Executive Summary: In a subchronic (13-week) subchronic toxicity study, Fischer 344 rats (10 sex/group) were exposed to concentrations of Telone II at 0, 10, 30, 90 or 150 ppm, 6 hours/day, 5 days/week for 13 weeks. Both sexes of rats at 90 and 150 ppm exhibited significant decreases in body weights while rats at 30, 60 and 150 ppm exhibited treatment-related histopathological lesions in the nasal turbinates. **The NOAEL was 10 ppm (0.045 mg/L) and the LOAEL was 30 ppm (0.136 mg/L), based on histopathological lesions in the nasal turbinates.**

Dose and Endpoint for Risk Assessment: HEC of 0.205 ppm (non-occupational risk assessment) or 0.86 ppm (occupational risk assessment) based on histopathological lesions in the nasal turbinates. The duration of exposure in the 13-week inhalation toxicity studies in rats is appropriate for this risk assessment. In addition, this study yields the lowest HEC of the studies available for consideration for this risk assessment. An UF of 30x defines HED's level of concern.

3.5.7.4 Long-term Inhalation Exposure

In a chronic toxicity/carcinogenicity study (MRID No. 40312301), B6C3F1 mice (50/sex/group plus 10/sex/group for the 6- and 12-month interim sacrifices) were exposed by whole-body inhalation to Telone II (92.1%) at concentrations of 0, 5, 20 or 60 ppm (equivalent to approximately 0, 0.023, 0.091 or 0.272 mg/L) 6 hours/day, 5 days/week for a total of 510 days over a two-year period. For chronic toxicity, the **NOAEL was 5 ppm (0.023 mg/L) and the LOAEL was 20 ppm (0.091 mg/L)** based on urinary bladder hyperplasia and hypertrophy/hyperplasia of the nasal respiratory mucosa.

Dose and Endpoint for Risk Assessment: HEC of 0.182 ppm (non-occupational risk assessment) or 0.77 ppm (occupational risk assessment) based on hypertrophy/hyperplasia of the nasal respiratory mucosa. The duration of exposure in the Chronic/Carcinogenicity toxicity study in mice is appropriate for this risk assessment. In addition, this study yields the lowest HEC of the studies available for consideration for this risk assessment.

3.5.8 Level of Concern for Margin of Exposure

When conducting inhalation risk assessments, the magnitude of the UFs applied is dependent on the methodology used to calculate risk. This risk assessment is based on the RfC methodology developed by the Office of Research and Development (ORD) for the derivation of RfCs and HECs for use in the MOE calculations. Since the RfC methodology takes into consideration the pharmacokinetic (PK) differences but not the pharmacodynamic (PD) differences, the UF for interspecies extrapolation may be reduced to 3X (to account for the PD differences) while the UF for intraspecies variation is retained at 10X. Thus, the UF when using the RfC methodology is customarily 30X.

Table 3.1. Summary of Levels of Concern for Risk Assessment.

Route	Short-Term (1 - 30 Days)	Intermediate-Term (1 - 6 Months)	Long-Term (> 6 Months)
Occupational (Worker) Exposure			
Dermal	N/A	N/A	N/A
Inhalation	30	30	30
Residential Exposure			
Dermal	N/A	N/A	N/A
Inhalation	30	30	30
Incidental Oral	N/A	N/A	N/A

For dietary and drinking water risk assessments, an UF of 100X is applied (10X for interspecies extrapolation, 10X intraspecies variation) since no dosimetric adjustments have been considered to translate the experimental NOAELs/LOAELs (from animal studies) to human equivalent doses. Consequently, the differences in PK and PD between animals and humans have not been accounted for in these risk assessments.

3.5.9 Classification of Carcinogenic Potential

3.5.9.1 Quantification of Carcinogenic Risk – Inhalation Exposures

The HED Cancer Peer Review Committee evaluated the toxicological database of 1,3-D and classified this chemical as “Likely to be carcinogenic to humans” based on the data from a 2-year inhalation bioassay in mice, where increased incidence of bronchioloalveolar adenomas were observed.

HED has adopted the Integrated Risk Information System’s (IRIS) method to derive the unit risk for inhalation exposure to1,3-D. The duration-adjusted HECs and tumor incidences were used to calculate the unit risk. **The Q_1* is 4 x 10^{-6} µg/m^3 or 1.8 x10^{-2} ppm^{-1}.**

3.5.9.2 Quantification of Carcinogenic Risk – Oral Exposures

The oral Q_1* for 1,3-D comes from the NTP studies where there were increased tumors in both sexes of rats (Fischer 344) and mice ($B_6C_3F_1$). The Q_1 * was revised in 1997 to 1.22 x 10^{-1} $(mg/kg/day)^{-1}$ and is based on forestomach, liver, adrenal, and thyroid tumors observed in male rats.

3.5.10 Recommendation for Aggregate Exposure Assessments

As per FQPA, 1996, when there are potential residential exposures to a pesticide, aggregate risk assessment must consider exposures from three major pathways: oral, dermal and inhalation exposures. Although 1,3-D is not used in residential settings, due to the volatility of 1,3-D residential exposure may occur when 1,3-D is applied to fields near residential areas. Accordingly, the only residential exposures will be inhalation exposures. Dietary exposure may occur from food from the proposed new use on grapes and from water as a result of the proposed new use and the existing pre-plant fumigations.

For the acute, short-, intermediate-, and long-term assessments the toxicity endpoints selected for inhalation and dietary exposures should not be aggregated since no common endpoints were identified at the LOAEL in studies conducted via the oral or inhalation routes. Although body weight gain decrements were observed in studies conducted by both routes (at the LOAEL in a chronic oral study and at a concentration above the LOAEL in the inhalation study), the magnitude of the effect noted in the inhalation study was minimal (≤11%) and was not considered toxicologically relevant. Thus, exposure through this route would not significantly contribute to the risk of eliciting body weight impairments after 1,3-D exposure. Additionally, the exposures via the inhalation route are much greater than dietary exposures, so contribution of the dietary exposures to the aggregate exposure is insignificant.

1,3-D has been classified as likely to be carcinogenic to humans via the oral and inhalation routes. However, the types of tumors observed in the inhalation and oral studies were different. Therefore, the oral and inhalation exposures should not be aggregated.

3.5.11 Summary of Toxicological Doses and Endpoints for 1,3-Dichloropropene for Use in Human Risk Assessments

Table 3.2. Summary of Toxicological Dose and Endpoints for Use in 1,3-Dichloropropene Dietary Risk Assessments

Exposure/ Scenario	Point of Departure	Uncertainty/ FQPA Safety Factors	Population Adjusted Dose	Study and Toxicological Effects
1,3-D Combined with Degradates: 3-Chloroallyl Alcohol and 3- Chloroacrylic Acid				
Acute Dietary Exposure (any Subpopulation)	NA	NA	NA	No hazard was identified attributable to a single exposure.
Chronic Dietary Exposure	NOAEL = 2.5 mg/kg/day UF = 100	UF_A= 10x UF_H=10x FQPA SF= 1x	Chronic PAD = 0.025 mg/kg/day	2- Year Combined Chronic/Carcinogenicity study -Rats LOAEL = 12.5 mg/kg/day Decreased body weight gain, increased incidence of basal cell hyperplasia of nonglandular stomach mucosa

Table 3.2. Summary of Toxicological Dose and Endpoints for Use in 1,3-Dichloropropene Dietary Risk Assessments				
Exposure/ Scenario	Point of Departure	Uncertainty/ FQPA Safety Factors	Population Adjusted Dose	Study and Toxicological Effects
Cancer (oral)	Classified as "likely to be carcinogenic in humans. Q_1 * = 1.22x 10^{-1} (mg/kg/day)$^{-1}$			2- Year Combined Chronic/Carcinogenicity study -Rats Combined forestomach, liver, mammary thyroid, adrenal, urinary, lung tumors, multistage model, 3/4 scaling factor.
UF = uncertainty factor. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. RfD = reference dose. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). NA = Not Applicable				

Table 3.3. Summary of Toxicological Dose and Endpoints for Use in 1,3-Dichloropropene Human Health Inhalation Risk Assessment (Non-Occupational)			
Exposure Scenario	**Point of Departure**	**HED HECs**	**Study and Toxicological Effects**
Acute	NOAEL = 454 ppm LOAEL = 583 ppm	75.67 ppm UF = 30	Acute Inhalation Studies -Rats Clinical signs, decreased body weight (mortality observed at ≥647 ppm)
Short-Term Inhalation (1 to 30 days)	NOAEL = 20 ppm (maternal) LOAEL = 30 ppm	5.0 ppm UF = 30	Developmental Inhalation Toxicity Study -Rabbit maternal decreased body weight gains
Intermediate -term Inhalation (1-6 months)	NOAEL = 10 ppm	0.205 ppm UF = 30	13-week inhalation in rats, nasal effects
Long-Term Inhalation (>6 months)	NOAEL = 5 ppm LOAEL = 20 ppm	0.182 ppm UF = 30	Chronic-Oncogenicity Study in Mice nasal histopathology
Cancer	Classification: Likely to be carcinogenic to humans Q_1 * = 4 x 10^{-6} ($\mu g/m^3$)$^{-1}$		
UF = uncertainty factor; EC = Human equivalent concentration; NOAEL = no observed adverse effect level; LOAEL = lowest observed adverse effect level; NA = Not Applicable			

Table 3.4. Summary of Toxicological Dose and Endpoints for Use in 1,3-Dichloropropene Human Health Inhalation Risk Assessment (Occupational)			
Exposure Scenario	**Point of Departure**	**HED HECs**	**Study and Toxicological Effects**
Acute	NOAEL = 454 ppm LOAEL = 583 ppm	227.0 ppm UF = 30	Acute Inhalation Studies -Rats Clinical signs, decreased body weight (mortality observed at ≥647 ppm)
Short-Term Inhalation (1 to 30 days)	NOAEL = 20 ppm (maternal) LOAEL = 30 ppm	15.0 ppm UF = 30	Developmental Inhalation Toxicity Study -Rabbit Maternal decreased body weight gains
Intermediate-Term Inhalation (1 to 6 months)	NOAEL = 10 ppm LOAEL = 30 ppm	0.86 ppm UF = 30	13-week Inhalation Toxicity -Rats Histopathological lesions in olfactory region of nasal cavity
Long-Term Inhalation (>6 months)	NOAEL = 5 ppm LOAEL = 20 ppm	0.77 ppm UF = 30	Chronic-Oncogenicity Study in Mice nasal histopathology
UF = uncertainty factor; HEC = Human equivalent concentration; NOAEL = no observed adverse effect level; LOAEL = lowest observed adverse effect level; NA = Not Applicable,			

3.6 Endocrine Disruption

EPA is required under the FFDCA, as amended by FQPA, to develop a screening program to determine whether certain substances (including all pesticide active and other ingredients) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." Following recommendations of its Endocrine Disruptor and Testing Advisory Committee (EDSTAC), EPA determined that there was a scientific basis for including, as part of the program, the androgen and thyroid hormone systems, in addition to the estrogen hormone system. EPA also adopted EDSTAC's recommendation that the Program include evaluations of potential effects in wildlife. For pesticide chemicals, EPA will use FIFRA and, to the extent that effects in wildlife may help determine whether a substance may have an effect in humans, FFDCA authority to require the wildlife evaluations. As the science develops and resources allow, screening of additional hormone systems may be added to the Endocrine Disruptor Screening Program (EDSP).

When additional appropriate screening and/or testing protocols being considered under the Agency's EDSP have been developed, 1,3-dichloropropene may be subjected to further screening and/or testing to better characterize effects related to endocrine disruption.

4.0 Public Health

An analysis of incidents related to 1,3-D use was completed by HED that considered data from the OPP Incident Data System, Poison Control Center, and California Pesticide Illness Surveillance Program. This analysis is provided below.

According to several reports in the Incident Data System, Poison Control Center, and California Pesticide Illness Surveillance Program, 1,3-D may cause skin injury described as blistering, burning sensation, or dermal irritation. All of the incidents, however, were related to accidental exposures resulting from spills due to equipment malfunctions or misuse (use of inadequate protective devices). Spills of 1,3-D have also been associated with respiratory effects in relatively large numbers of people in the vicinity of the spill as reviewed by Albrecht (1987).

One report obtained from the Incident Data System described an incident in which 1,3-D was injected into the soil and twelve residents in two adjacent houses reported burning/watery eyes and sore throats. One child reported coughing. The report further states that the applicator complied with the established 100 foot buffer zone; however, the buffer was insufficient to prevent symptoms among residents living adjacent to the field. As a result of this incident, the County Agricultural Commissioner (CAC) "conditioned the permit for fumigant use at the site to require written notice to the occupants and maintenance of a 300-foot buffer zone."

HED has recently produced an update as of March 16, 2007 that focuses on incident data collected from CDPR, Poison Control Centers, NIOSH SENSOR, and other 6(a)(2) data. This update can be found below. [Note: HED is also in the process of preparing a comprehensive incident data assessment for seven soil fumigants, including 1,3-D].

(1) California data. From 2002-2004, California occupational surveillance data contained a total of 101 new incidents for 1,3-D, all occurring in 2004. By comparison, for three other soil fumigants

over the same time period, there was a downward trend over time. Metam–sodium had a total of 428 (’02=384, ‘03=61 and ‘04=4) reported incidents; Chloropicrin had 192 total incidents (‘03=191, ‘04=1) and Methyl Bromide had 413 total incidents (‘02=391, ‘03=18, and ‘04=4) incidents. The downward trend for three of four soil fumigants suggests the possibility of positive results from worker outreach/education and/or CDPR regulatory changes. However, the fact that the 1,3-dichloropropene incidents were seen to increase at 101 incidents in ’04 suggests the possibility of use pattern changes. Reasons for the temporal patterns observed are being further explored with CA DPR incident data providers.

(2) NIOSH SENSOR data: Currently, twelve states report occupational poisoning incidents to a central database. The states are CA, WA, OR, NY, AZ, LA, TX, NM, FL, NC, MI, IA. For the time period ’98-’03 covering 5899 total incident cases, 3 incidents were for 1,3-D, including all males. States reporting are as follows: CA=1 incident, LA=1, an MI=1. Underreporting is a known problem from the literature. Due to underreporting, there are generally few duplicates found among the multiple data sources. Matching the exact dates, locations, and other incident case details eliminates duplicate incident cases.

(3) Poison Control Center (PCC) data: This is the only source of National incident coverage, encompassing 61 poison centers that report in a standard format. Only PCC reports data on children, as well as occupational and non-occupational cases, symptom severity and medical outcome, including death. For the time period ’92-’05, PCC reported 66 1,3-D incidents, 24 occupational, 40 non-occupational, and 3 children. There were no deaths reported in recent years.

(4) 6(a)(2) and other data: A comprehensive incident data assessment for seven soil fumigants, including 1,3-D is in preparation. 1,3-D [Telone, Telone II, D-D (dichloropropene)] was among the fumigants studied in the interagency Agricultural Health Study (AHS), (see www.aghealth.org). No chemical specific reports have been published to date on 1,3-D. When published, these results and results from the other data sources will be used to update the EPA assessment.

In summary, at a time when other soil fumigant incidents declined in CA (2002-2005), possibly due to a combination of changing use patterns, state/local regulatory changes, and/or better worker education and outreach, there were 101 1,3-D CA incidents in (2004). CADPR in their 2003 annual accomplishments reported doing ten outreach trainings with growers and applicators. These sessions were designed to prevent large-scale incidents.

5.0 Dietary Exposure/Risk Characterization

5.1 Pesticide Metabolism and Environmental Degradation

5.1.1 Metabolism in Primary Crops

The qualitative nature of the residue in plants is adequately understood based on soybean, tomato, and sugar beet metabolism studies. Although the studies involved pre-plant applications, they were conducted at application rates more than 20 times the rate proposed for this use. In studies with tomatoes and soybean, no parent, 3-chloroallyl alcohol (CAAL), or 3-chloroacrylic acid (CAAC) metabolites were detected, and incorporation into natural plant constituents was demonstrated. In the study with sugar beets, parent and metabolites were also not detected, and the parent compound was shown to have been metabolized and incorporated into sucrose.

5.1.2 Metabolism in Rotational Crops

An acceptable confined rotational crop study was conducted with wheat, lettuce, carrots, and radishes. The results were in agreement with those from primary plant metabolism studies, showing extensive incorporation of radiolabelled residues into natural plant biochemical constituents. No plant-back restriction is required.

5.1.3 Metabolism in Livestock

There are no livestock feed items associated with this request; therefore, no residue chemistry data are required under this guideline topic.

5.1.4 Analytical Methodology

The method submitted for the determination of parent is suitable for data collection and enforcement. The method submitted for the determination of CAAL and CAAC is acceptable for data collection and is tentatively acceptable for enforcement. An independent laboratory validation (ILV) for the metabolite method, Method GRM 99.18, is required to confirm that it is suitable for tolerance enforcement. Multi-residue method data are not available for 1,3-dichloropropene. These data are required for the parent and metabolites.

5.1.5 Environmental Degradation

The *cis* and *trans* isomers of 1,3-dichloropropene (1,3-D) are highly volatile and mobile under most environmental conditions. The major hydrolysis degradates, 3-chloroallyl alcohol and 3-chloroacrylic acid, are both mobile and persistent. The primary routes of 1,3-D dissipation in the field appear to be volatilization, leaching, abiotic hydrolysis, and aerobic soil metabolism. In air, 1,3-D does not degrade through direct photolysis; however, there can be degradation through free-radical (OH and ozone) processes. In water, hydrolysis is temperature dependent with an increase in stability at lower temperatures. This seems to indicate that in warm climates, degradation will occur more rapidly than in cooler climates. According to laboratory mobility studies, 1,3-D is mobile in a variety of soils including loamy sand (K_d= 0.23) and sand (K_d= 0.32). 1,3-D is also mobile in clay soils (K_d= 0.42 and 1.09) which is highly unusual for most pesticides. These mobility data, in addition to ground-water monitoring information, have clearly demonstrated that 1,3-D is highly mobile in soil.

As mentioned above, 1,3-D is highly volatile. The factors influencing the volatility of 1,3-D from a field plot include, but are not limited to: soil organic matter, wind speed, soil moisture content, depth of incorporation-injection, soil temperature and soil porosity. Wind is a major factor in the dispersion of 1,3-D as higher concentrations are measured at night. During the day, an increase in wind velocity also increases vapor dispersion and lowers the measurable amount of material.

1,3-D has two major degradates: *cis* and *trans* isomers of 3-chloroallyl alcohol and 3-chloroacrylic acid. The 3-chloroallyl alcohol is the major hydrolysis degradation product and is formed at 72% of applied. The 3-chloroacrylic acid is produced through aerobic soil metabolism at lower and variable amounts depending on the soil type. In studies submitted to the Agency, 3-chloroacrylic acid formed at 1% - 6% of applied.

The most recent risk assessment (C. Olinger, 6/6/07) included consideration of drinking water exposure to a manufacturing impurity, 1,2-dichloropropane. The registrants have modified the manufacturing process to reduce the concentration of the impurity. HED has recently reviewed the Confidential Statements of Formula (CSFs) for all technical registrants of 1,3-D, and none list 1,2-dichloropropane as an impurity greater than 0.1% (C. Olinger, 12/14/07). Therefore, EFED and HED no longer have any concerns over the potential for 1,2-dichloropropane to reach drinking water, and all risk estimates have been removed from the risk assessment.

5.1.6 Toxicity Profile of Major Metabolites and Degradates

In December 2004 members of the 1,3-D risk assessment team met to discuss the toxicity of the 1,3-D degradates, the *cis* and *trans* isomers of 3-chloroacrylic acid and 3-chloroallyl alcohol. The acute and subchronic toxicity studies indicate that the toxicity of the degradates is within the same order of magnitude as the parent compound and generally exhibit similar effects at high doses. 1,3-D has been shown to be mutagenic in bacteria and mammalian cell lines, has the ability to form reactive epoxides, and is carcinogenic in rats and mice. The limited data on CA-alcohol and CA-acid provide conflicting evidence that the degradates are weakly or non-mutagenic. Nevertheless, the ability to form the same reactive epoxide is a possibility of the degradates. For these reasons, the degradates will continue to be included in the chronic and cancer dietary exposure and risk assessments.

5.1.7 Pesticide Metabolites and Degradates of Concern

Table 5.1 Summary of Metabolites and Degradates to be included in the Risk Assessment and Tolerance Expression

Matrix		Residues included in Risk Assessment	Residues included in Tolerance Expression
Plants	Primary Crop	*cis* and *trans* isomers of the parent, 3-chloroallyl alcohol, and 3-chloroacrylic acid	*cis* and *trans* isomers of the parent, 3-chloroallyl alcohol, and 3-chloroacrylic acid.
	Rotational Crop	Not Applicable	Not Applicable
Livestock	Ruminant	Not Applicable	Not Applicable
	Poultry	Not Applicable	Not Applicable
Drinking Water		*cis* and *trans* isomers of the parent, 3-chloroallyl alcohol, and 3-chloroacrylic acid	Not Applicable

5.1.8 Drinking Water Residue Profile

Surface Water Sources. The Agency currently lacks sufficient surface water-related exposure data from monitoring to complete a quantitative drinking water from surface water exposure analysis for 1,3-D. Therefore, the Agency is presently relying on model-generated Estimated Drinking Water Concentrations (EDWCs). The maximum application rates and relevant environmental fate parameters for 1,3-D were used in the screening model PRZM/EXAMS for EDWCs in surface water. The output of the screening model represent estimates of the concentrations that might be

found in surface water due to the use of 1,3-D as a pre-plant soil fumigant and are presented in Table 5.2. The concentrations of the degradates 3-chloroallyl alcohol and 3-chloroacrylic acid, were estimated as well. The EDWCs from the existing pre-plant fumigation uses was used as a screening level assessment for drinking water exposure because the application rate is approximately 20x that of the proposed new use, and the FQPA requires the Agency to consider all exposures when setting tolerances.

With respect to 1,3-D, preliminary results of an "edge-of-field" runoff study conducted in the tobacco growing region of Virginia indicate that a small percentage (less than 0.003 percent) of the total mass of 1,3-D applied reaches surface water under a high-end simulated runoff scenario shortly after application. Limited USGS National Water Quality Assessment (NAWQA) surface water monitoring data are available for 1,3-D and its degradates. NAWQA data available from several high use states (CA, FL, ID, OR and WA) showed no detects in 123 samples.

Although the Environmental Fate and Effects Division (EFED) has provided modeled EDWCs for use in the drinking water exposure assessment, they have also characterized the estimate as an overestimate of actual drinking water concentrations (Eckel, 2008). As described in Section 5.1.5, the major dissipation process for 1,3-D is volatilization. The volatilization routines in PRZM were improved in the most recent version that EFED uses (3.12.2, dated May 12, 2005), but still only model volatilization at room temperature and it has not been subjected to a quality assurance review to ensure that it performs as expected. Volatilization will be faster at summer outdoor temperatures, so this important process is not captured adequately. Thus, PRZM-EXAMS does not adequately model the major dissipation process for 1,3-D. The usefulness of PRZM-EXAMS exposure estimates is also limited by the quality and quantity of the input data describing the fate processes. The current database for 1,3-D is not adequate to do a refined exposure assessment. The lack of aerobic aquatic metabolism data and soil metabolism studies on additional soils has led to overestimates of degradation rates (i.e. much slower degradation rates than the limited available data suggest) that would lead to overestimates of modeled drinking water outputs. Also, data on the indirect photolysis of 1,3-D are not available, and information on reactions with hydroxyl radicals in air indicate that this could be an important route of dissipation in water. EFED has requested additional environmental fate data that would allow further refinement of the surface water assessment.

Groundwater Sources. Sufficient data for tap water from groundwater wells are available for 1,3-D and its degradates 3-chloroacrylic acid (CAAC) and 3-chloroallyl alcohol (CAAL). A total of 518 wells were selected in the Central Columbia Plateau, Upper Snake River Basin, North Platte River, Albermarle-Pamlico Sound, and the Georgia/Florida basins. The wells were intended to be among the most vulnerable wells available for sampling in each region because they were in high use areas, were among the shallowest in each region, and were located in close proximity to fields that had received 1,3-D application in the recent past. 1,3-D and its two metabolites were not found above 0.145 ppb in 5,800 samples. A total of 65 of 518 measured taps demonstrated detectable (>0.015 to 0.023 ppb) levels of 1,3-D or one of its metabolites at some point during the study, with only three wells having more than one detection (maximum was two detections). To be conservative, in all chronic calculations, the Limit of Detection was used when the chemical was "not detected." As a point of comparison, the modeled estimates of 1,3-D in groundwater using SCI-GROW, ranged from 738 ppb to 1340 ppb. Like the surface water model, SCI-GROW is not designed for highly volatile chemicals such as 1,3-D and its degradates.

Table 5.2. Estimated Drinking Water Concentrations for 1,3-D in Surface Water and Groundwater		
Chemical	Surface Water (μg/L)	Groundwater (μg/L)
	Cancer/chronic	Cancer/chronic
Combined 1,3-D and Degradates [1,3]	16.2	0.14 [2]

[1] Estimated drinking water concentrations are based on PRZM/EXAMS data.
[2] Estimated drinking water concentrations are based on monitoring data and include parent and degradates.
[3] Degradates include cis and trans isomers of both 3-chloroallyl alcohol and 3-chloroacrylic acids

5.1.9 Food Residue Profile

Thirteen crop field trials were conducted to support this use and were conducted at exaggerated rates, at a seasonal rate approximately five times the rate of the pre-harvest application rate. The field trials are representative of typical grape growing areas in the US, as most of the trials were conducted in California, two in Washington, and two in New York. Most of the pre-harvest intervals ranged from 6-30 days, which is considerably shorter than the proposed 60-day PHI. The analytical methods used were appropriate for the parent and metabolites and showed good recoveries. The residue data are not supported by adequate storage stability data, although supplemental data on soybeans give some indication of stability for the storage intervals of the submitted study. The residue data are sufficient to support the proposed use, provided the registrant submits a grape storage stability study for all residues of concern, which reflects a minimum storage interval of 154 days.

Residues of the parent (*cis* and *trans* isomers) were non-detectable (at an LOD of approximately 0.9 ppb) in all trials with a pre-harvest interval exceeding 21 days. Residues of the metabolites 3-chloroacrylic acid (CAAC) and 3-chloroallyl alcohol (CAAL) were generally non-detectable at most sites at all pre-harvest intervals with the exception of one trial in Washington and one trial in California.

Residues of the metabolite 3-chloroacrylic acid (CAAC) were non-detectable at all sites and all PHIs with the exception of the samples from one Washington trial. Residues of *cis*-CAAC were detectable but below the LOQ of 0.003 ppm at a PHI of 74 days. Residues of *cis*-CAAL were detectable at all PHIs at this site as well up to a level of 0.005 ppm. *Cis*-CAAL was also detected at one CA site at a PHI of 28 days, but residues were below the LOQ of 0.003. Residues of *trans*-CAAC and *trans*-CAAL were not detectable at any site at any PHI.

These trials reflect four pre-harvest applications at rates of approximately 1.3 times the proposed single application rate and pre-harvest intervals much shorter than the proposed uses. The proposed use directions specify only one application prior to harvest. HED does not expect quantifiable residues when 1,3-D is used in accordance with the use directions, and is recommending for a tolerance at the combined limits of quantitation for all of the residues of concern, or 0.018 ppm. The residue data show that the actual residues are likely to be considerably lower.

Processing studies are not available. However, none are required as exaggerated rate data showed that is unlikely that residues at the proposed PHI will be detectable. Due to the volatile nature of the residues of concern, residues are likely to dissipate during processing. However, should residues concentrate during processing, they will be below the recommended tolerance.

5.1.10 International Residue Limits

There are no Canadian or Codex Maximum Residue Limits for residues of 1,3-dichloropropene in any commodity.

5.2 Dietary Exposure and Risk

1,3-Dichloropropene chronic and cancer dietary exposure assessments were conducted using the Dietary Exposure Evaluation Model software with the Food Commodity Intake Database (DEEM-FCID™, Version 2.03), which incorporates consumption data from USDA's Continuing Surveys of Food Intakes by Individuals (CSFII), 1994-1996 and 1998. The 1994-96, 98 data are based on the reported consumption of more than 20,000 individuals over two non-consecutive survey days. Foods "as consumed" (e.g., apple pie) are linked to EPA-defined food commodities (e.g. apples, peeled fruit - cooked; fresh or N/S; baked; or wheat flour - cooked; fresh or N/S, baked) using publicly available recipe translation files developed jointly by USDA/ARS and EPA. For chronic exposure assessment, consumption data are averaged for the entire U.S. population and within population subgroups, but for acute exposure assessment are retained as individual consumption events. Based on analysis of the 1994-96, 98 CSFII consumption data, which took into account dietary patterns and survey respondents, HED concluded that it is most appropriate to report risk for the following population subgroups: the general U.S. population, all infants (<1 year old), children 1-2, children 3-5, children 6-12, youth 13-19, adults 20-49, females 13-49, and adults 50+ years old.

For chronic dietary exposure assessment, an estimate of the residue level in each food or food-form (e.g., orange or orange juice) on the food commodity residue list is multiplied by the average daily consumption estimate for that food/food form to produce a residue intake estimate. The resulting residue intake estimate for each food/food form is summed with the residue intake estimates for all other food/food forms on the commodity residue list to arrive at the total average estimated exposure. Exposure is expressed in mg/kg body weight/day and as a percent of the chronic population adjusted dose (cPAD). This procedure is performed for each population subgroup.

5.2.1 Acute Dietary Exposure/Risk

No appropriate endpoint attributable to a single exposure (dose) was identified from oral toxicity studies for females 13+ or the general population.

5.2.2 Chronic Dietary Exposure/Risk

HED is concerned when dietary risk exceeds 100% of the PAD. The DEEM-FCID™ analyses estimate the dietary exposure of the U.S. population and various population subgroups. The results of the chronic dietary analyses are reported in Table 5.3. The dietary exposure is less than 1% of the population adjusted dose for all population groups for food alone and food plus tap water from ground water sources, and is less than 5% of the population adjusted dose for all population groups

for food plus water from surface water sources. The most highly exposed sub-group is infants, if the surface water value is used, and children aged 1-2 if the tap water value is used.

Table 5.3. Summary of Chronic Dietary Exposure and Risk for 1,3-Dichloropropene						
Population Subgroup	**Chronic Dietary Food Only**		**Chronic Dietary Food and Water – Ground Water Sources [2]**		**Chronic Dietary Food and Water [2] - Surface Water Sources**	
	Dietary Exposure (mg/kg/day)	**% cPAD[1]**	**Dietary Exposure (mg/kg/day)**	**% cPAD[1]**	**Dietary Exposure (mg/kg/day)**	**% cPAD[1]**
General U.S. Population	0.000003	<1	0.000006	<1	0.000344	1.4
All Infants (< 1 year old)	0.000005	<1	0.000015	<1	**0.00112**	**4.5**
Children 1-2 years old	**0.000016**	**<1**	**0.00002**	**<1**	0.000523	2.1
Children 3-5 years old	0.00001	<1	0.000014	<1	0.000484	1.9
Children 6-12 years old	0.000004	<1	0.000007	<1	0.000331	1.3
Youth 13-19 years old	0.000001	<1	0.000003	<1	0.000248	1.0
Adults 20-49 years old	0.000002	<1	0.000005	<1	0.000321	1.3
Adults 50+ years old	0.000002	<1	0.000005	<1	0.000337	1.3
Females 13-49 years old	0.000002	<1	0.000005	<1	0.000319	1.3

[1] The values for the highest exposed population are bolded.
[2] The tap water value (0.14 μg/L) was used in this assessment for ground water exposure and 16.2 μg/L for the drinking water from surface water sources.

5.2.3 Cancer Dietary Risk

HED is generally concerned when cancer risks exceed 1 x 10^{-6}. Because of the uncertainties regarding estimation of cancer potency and human exposure, risk estimates ranging from 1 to 3 x10^{-6} are generally considered indistinguishable. The results of the cancer dietary risk analyses are presented in Table 5.4. The estimated cancer risk for food alone and food and drinking water from groundwater sources is below HED's level of concern for 1,3-D and its degradates.

Although risk for drinking water from surface water sources for 1,3-D exceeds the negligible standard, based on characterization of the model estimates provided by EFED, HED considers the risk estimates to be an overestimate, and likely to be no more than those of ground water sources. As discussed in Section 5.1.8, the surface water model, PRZM-EXAMS is not designed for chemicals such as 1,3-D where volatilization is the primary route of dissipation. Insufficient data are available to further refine the inputs to the model, leading to the assumption of much slower degradation in the environment by the model than is likely. The limited surface water monitoring data available for high use areas did not show any detects of 1,3-D and its degradates.

Historically, EFED's concern about exposure to 1,3-D in drinking water has been from ground water exposure sources. This is due to very high application rates (hundreds of pounds per acre) for the existing pre-plant fumigation uses, and its high mobility in soil (and thus potential to leach to ground water). Once introduced into ground water, 1,3-D is shielded from many of the processes that can contribute to its more rapid dissipation from surface water. These include photolysis, volatilization to the atmosphere from the surface of water bodies, volatilization due to the motion of flowing water (both during run-off and stream flow), and the greater availability of oxygen for biological

metabolism. All of these processes combined make it likely that exposure from surface water sources will be less than that from ground water sources (Eckel 2008). Because the cancer risk from ground water sources is below the Agency's level of concern without the benefit of these processes to aid dissipation, HED believes that the cancer risk from surface water sources will also be below the Agency's level of concern based on its likely dissipation from surface water sources.

Table 5.4. Summary of Cancer Dietary Exposure and Risk for 1,3-Dichloropropene

Population Subgroup	Chronic Dietary Food Only		Chronic Dietary Food and Water [1]	
	Dietary Exposure (mg/kg/day)	Risk	Dietary Exposure (mg/kg/day)	Risk
General U.S. Population – 1,3-D and degradates – ground water sources for drinking water	0.000003	3×10^{-7}	0.000006	7×10^{-7}
General U.S. Population – 1,3-D and degradates– surface water sources for drinking water	0.000003	3×10^{-7}	0.000344	4×10^{-5}

[1] The tap water value (0.14 µg/L) was used in this assessment for ground water exposure and 16.2 µg/L (combined 1,3-D and degradates) for the drinking water from surface water sources for combined 1,3-D and degradates.

5.3 Anticipated Residue and Percent Crop Treated (%CT) Information

The dietary assessment assumes all grapes consumed in the US are treated with 1,3-dichloropropene. Residues of the parent compound isomers and three of the four degradates were assumed to be at ½ the limit of detection (0.001 ppm) since residues were non-detectable in all field trials at shorter pre-harvest intervals (PHI) than the proposed use. Residues at the proposed PHI in one trial of one degradate were at the limit of quantitation (0.003 ppm), so the LOQ was used. The degradates were assumed to have equal toxicity to the parent compound, so the total anticipated residue used in the dietary assessment for the chronic and cancer analyses was 0.0055 ppm.

6.0 Non-Occupational Exposure Assessment and Characterization

This section describes the potential exposure scenarios associated with the post-plant use of 1,3-D. [Note: 1,3-D is also registered for pre-plant agricultural uses. For details of the bystander exposure related to the existing uses, please see the Phase 5 1,3-D RED]. These include residential bystander exposure from two key sources: known sources (e.g., at the edge of a treated field), as well as from many sources within a region (e.g., ambient air). There are no residential uses of 1,3-D by homeowners so this aspect of the risk assessment focuses on those types of exposures that may occur to bystanders resulting from agricultural uses of 1,3-D.

Residential bystander exposure may occur because of emissions from treated fields. These emissions can travel to non-target areas and will be referred to simply as bystander risks in this assessment. Bystander exposures can occur as a result of being in contact with residues that were emitted from a known source (near field) and also from multiple sources within a localized region (ambient). For clarity, a known source in this assessment is intended to represent area sources from a single application (e.g., a treated farm field). Exposures from near field sources for bystanders

(resulting from the proposed use) are described below in Section 6.1 and ambient air exposures are described below in Section 6.2.

6.1 Bystander Exposures And Risks From Near Field Sources

The Agency's calculation of bystander exposures and risks from known sources has been an iterative process based on the ability to provide additional predictive capabilities yet consider all possible sources of information that could be used to characterize the overall risk picture associated with a chemical. This approach is also consistent with general Agency guidance on the use of air models.

Three main sources of information have been used for assessing bystander risks. Each source has a unique level of predictive capability but each result has been carefully considered in context with each other in order to develop an overall characterization of the risks associated with 1,3-D use. Each method is described in detail in *Section 6.1.1 from the Phase 5 RED.: Methods Used To Calculate Bystander Exposures And Risks From Known Sources* along with a description of how they were used and how they should be interpreted in the context of this assessment. Regardless of which approach is utilized, it is clear that there can be possible human health effects associated with the use of soil fumigant chemicals based on calculated risk estimates.

Exposures to bystanders from a single post-plant drip irrigation fumigation and their associated risks, calculated using the PERFUM modeling approach, have been used to assess the new use of 1-3,D and they are presented in this section. These exposures were also analyzed using the actual field study data (i.e, the Monitoring Method. See appendices for further details pertaining to these analyses). Because of the refinements offered by the modeling approaches, it is believed that those results should be considered as the most appropriate for evaluating the risks associated with 1-3,D applications.

Appendices C through E contain the following information:

- Appendix C. PERFUM Analysis: Appendix D summarizes the results of the analysis (i.e., various combinations of meteorological data and flux/application methods) and provides a summary of outputs generated by PERFUM for the 1,3-D product, Telone II. It does not contain detailed input and output files needed to complete calculations with PERFUM. If so required, these can be provided for review and validation purposes. It should be noted that PERFUM results for all products yield the same results and were not produced for each product.
- Appendix D. Analysis of Data for Agricultural Field Uses: Appendix E contains the analysis of the available 1,3-D monitoring data. [Note: This appendix also contains a summary table that provides risk calculations based on the data.]
- Appendix E. Model Information and History.

The analyses which were completed using PERFUM are based on combinations of flux and meteorological data. In addition, the impact of field size and shape, application rates, "whole vs. maximum buffer" statistics, and target concentrations (i.e., HECs coupled with uncertainty factor) were evaluated. The field sizes and shapes that were considered include:

- 1 acre (square, rectangle oriented on its side, rectangle oriented on its end);

- 40 acres (square).

The application rates that were considered include 100 percent of the maximum rate and, to evaluate a range, 75, 50, and 25 percent of the application rate were also considered. [Note: PERFUM outputs for the 25 percent rate were generated and are available but not summarized at this point.] In all cases, results for both maximum and whole buffer statistics were evaluated to allow for a broader range of risk characterization.

The risk estimates presented below represent results for the acute duration of exposure because they compare 24 hour concentrations calculated with PERFUM to the acute HEC. Results for selected percentiles of exposure are reported. Additional analysis based on other percentiles of exposure could be completed if so needed.

It should be acknowledged that a myriad of micro-environmental conditions and factors can impact how 1,3-D will volatilize and disperse from any given treated field on a particular day. With this premise, it would be logical to evaluate basic factors which could influence flux (e.g., soil type, soil temperature, percent water, etc.) and also micro-climates (e.g., topography) and thus ultimately impact results. PERFUM, however, cannot easily address specific changes in these factors because it is not a 1st Principles Model where the approach would be to build a predictive tool from basic fate characteristics. Instead, PERFUM is an empirical model which utilizes field study and actual meteorological data to predict results and since field study data are the basis for the PERFUM predictions it follows that results based on empirical monitoring and those calculated with PERFUM would be similar (see guidance pertaining to air model validation at http://www.epa.gov/scram001/guidance/guide/appw_03.pdf for additional information).

It should also be acknowledged that the nomenclature incorporated into PERFUM uses the term "buffer zone" which equates to the distance downwind at which a specific target concentration (i.e., combination of HEC and UF) is met based on the desired statistical parameters. The use of this term does not imply any regulatory decision. In the context of this risk assessment, it should only be considered as the predicted distance for a specific target concentration. A number of differing factors were considered to evaluate the sensitivity of the results to changes in various inputs.

It is clear that given the number of possible permutations of PERFUM inputs and ways of presenting the outputs that there are many possible approaches for interpreting the results. The central goal, however, is to quantify how potential risks change with factors such as application method, distance from the treated field, percentile of exposure, selected statistical basis (i.e., whole vs. maximum buffer approach), application rate, and field size/shape. Each of these factors has been considered and very detailed results pertaining to each are available in the appendices referenced above.

Table 6.1 summarizes the results for the combination of Ventura California meteorological data and post-plant drip irrigation field volatility study on vineyard grapes (MRID #45296101). Similar to the results for the pre-plant uses of 1,3-D, the PERFUM modeling results for post-plant vineyard use indicates that acute risk do not exceed HED's level of concern at 0 meters from treated fields. The Agency has some concerns with the quality of this study. First, the application rate used in the study was 5.4 lbs ai/acre, while the maximum application rate allowable is 17.7 lbs ai/acre. In general, the Agency believes that scaling down from the maximum application rate is acceptable, assuming a linear relationship between application rate and flux rate. The Agency has concerns with the practice of scaling up flux rates to the maximum application rate, as it is unclear if soil saturation may occur that causes more off-gassing (flux) than expected. Additionally, while flux rates were calculated from this study data, the regression analysis for most periods yielded poor r-squared values and reordering of the data was required. This is a standard practice, but a better designed study probably would have yielded better results. A smaller field and samplers placed closer to the edges of the field (e.g., the samplers in this study were roughly 300 ft away - most studies have samplers around 30 ft away) would have produced a higher quality of data. As a result, the Agency has low confidence in the flux rates obtained from this study.

However, since the risk estimates for the 1,3-D pre-plant drip agricultural uses (all of which are applied at much higher application rates) are not of concern at 0 meters from treated fields, and the proposed label specifies a buffer zone of 100 ft, the Agency expects that the post-plant vineyard use will not pose a risk of concern for bystanders.

Table 6.1 Buffer Distances for Ventura CA Weather and Post-Plant Drip Irrigation Flux

Percentiles	Max (17.75 lb ai/A)		75% (13.31 lb ai/A)		50% (8.87 lb ai/A)	
	1 Acre Square	40 Acre Square	1 Acre Square	40 Acre Square	1 Acre Square	40 Acre Square
Maximum Buffer Distances (meters)						
50	0	0	0	0	0	0
75	0	0	0	0	0	0
90	0	0	0	0	0	0
95	0	0	0	0	0	0
97	0	0	0	0	0	0
99	0	0	0	0	0	0
99.9	0	0	0	0	0	0
99.99	0	0	0	0	0	0
Whole Field Buffer Distances (meters)						
50	0	0	0	0	0	0
75	0	0	0	0	0	0
90	0	0	0	0	0	0
95	0	0	0	0	0	0
97	0	0	0	0	0	0
99	0	0	0	0	0	0
99.9	0	0	0	0	0	0

Table 6.1 Buffer Distances for Ventura CA Weather and Post-Plant Drip Irrigation Flux						
Percentiles	Max (17.75 lb ai/A)		75% (13.31 lb ai/A)		50% (8.87 lb ai/A)	
	1 Acre Square	40 Acre Square	1 Acre Square	40 Acre Square	1 Acre Square	40 Acre Square
99.99	0	0	0	0	0	0

6.2 Ambient Bystander Exposure from Multiple Regional Sources

Ambient levels of 1,3-D are not attributable to a specific application event; rather, contributions to the ambient samples may occur from multiple sources. For example, it is possible that bystanders could be exposed to 1,3-D air emissions resulting from applications to multiple fields in a geographic area, particularly if they live in or frequent agricultural areas where there is significant use, such as in a strawberry growing region of California.

Exposures from ambient air that occur from multiple regional sources of 1,3-D were estimated from monitoring data collected to represent conditions at a regional level. The California Air Resources Board (CARB) generated most of the data considered in this analysis. CARB is a widely recognized institution for these types of programs and it is part of the California Environmental Protection Agency. CARB conducts air monitoring studies for various types of chemicals throughout California. These studies conducted by CARB can generally be categorized as one of two types including: (1) targeted monitoring typically completed upon request to provide information related to specialized issues such as fumigant exposures in areas of high use during the season of use; and (2) routine monitoring for select pollutants via established networks in order to better quantify exposures in the general population (i.e., CARB established its Toxic Air Contaminant monitoring program or TAC for routinely quantifying toxic chemicals in air in urban areas).

For ease and clarity, the HED has opted by convention to describe the available ambient bystander data used in this assessment as follows:

(1) "CARB Data": includes targeted monitoring data generated by CARB focused on areas of high 1,3-D use in the season of use; and

(2) "TAC Data": includes data from CARB's Toxic Air Contaminant Network for 1,3-D that quantifies background levels in non-agricultural, urban environments.

6.2.1 Exposures from Targeted Regional Ambient Source Air Monitoring

For the targeted ambient air analysis, HED evaluated different durations of exposure with data ranging from single day acute exposures to chronic exposures.

Samples were collected 1 to 4 times per week from each station over the course of the use season. For the 24 hr TWA results, the values are the maximum values monitored. Targeted ambient air monitoring was done for 7 to 9 weeks during season of high use in California. The monitoring period was 7 weeks for Kern County in 2000 and 9 weeks for Kern County in 2001. Samples were taken for 8 weeks in Monterey and Santa Cruz Counties in 2000 and 2001.

The exposure concentrations for these intervals have been reported as the mean weekly means for samples collected during each calendar week over the course of the use season. This approach was taken in order to statistically weigh equally each week's contribution to the overall seasonal mean because of differing numbers of samples in some weeks. Concentrations over the course of a season monitored in these studies did not vary extensively so calculation of average concentrations for shorter durations (e.g., 4 weeks) or even the use of an overall mean of all samples are not expected to be dramatically different estimates used in this assessment. It should be noted that the statistical summaries of the available data were completed by DPR and that the Agency reviewed and concurred with this approach. There are many possible ways to calculate exposure estimates given the available data for completing a short- and intermediate-term assessment. For example, a TWA over an entire season could be calculated or weekly TWAs could be calculated and then averaged over a season. The Agency agrees with DPR's use of the mean of weekly means because it does not weigh results for the number of samples collected in a week (i.e., most weeks had 4 samples but some had 3) and it does not require a data filling procedure for the days missing each week (i.e., usually Wed., Sat., and Sun with most applications early in the weekend because of near school buffer issues).

For the targeted ambient monitoring data, the acute Margins of Exposure (MOEs) are calculated by comparing the maximum 24 hour TWA to the acute HEC. For short- and intermediate-term risks, MOEs are calculated by comparing the mean of weekly mean estimates (as calculated by CDPR) to the HEC selected for short- and intermediate-term exposure. Since sampling was done in the high use season, air concentrations used for risk assessment are expected to be protective for exposures which could occur throughout the year.

Chronic exposure estimates were also calculated using the targeted regional source ambient data. These calculations should be considered as rangefinder estimates of exposure only, because of a lack of monitoring studies specifically designed for this purpose. Specifically, short- and intermediate-term estimates were amortized to reflect a potential for exposure of 180 days out of each calendar year in order to calculate chronic estimates of exposure. This was based on the approximate use patterns for 1,3-D over a year in high use areas. Results based on all of these calculations, as indicated above, do not represent a risk concern to the Agency and in most cases risks were far below the target level of concern (e.g., by orders of magnitude). There were no ambient monitoring studies targeting areas of high use that collected air samples over an entire year that would be considered representative of a chronic exposure pattern. In these studies the focus was more on the actual season of use so these data were typically collected for only 9 weeks or so which represents the duration of the typical application season. However, in order to be able to evaluate the possibility of chronic exposures in high use areas the Agency utilized the seasonal mean of means from the high use areas and supposed that exposures could be maintained at this rate for a sustained period of 6 months which is twice as long as a normal application season. This approach does have some uncertainty associated with it but the Agency believes that this approach does not underestimate exposure because monitoring data were collected in the season of use in areas of high use. Additionally, risks calculated based on this method, as indicated above, are typically well below the Agency's level of concern. In addition to using the targeted monitoring data, the Agency also used the urban background monitoring data to calculate chronic risks. In this case, the data were intentionally designed to be used to evaluate longer-term exposure levels. Many of the samples collected in this network did not even contain measurable residues over the course of the monitoring years in question but chronic risks were still evaluated as a precautionary measure. As indicated

above, risks based on these results tended to be at least two orders of magnitude lower that the Agency's level of concern.

For cancer risk assessment, the lifetime average daily exposure (LADE) is calculated using the mean of weekly means and assumes that exposure lasts the length of the longest monitoring period (9 weeks / 63 days). Cancer risk is then calculated by multiplying the LADE by the non-occupational Q_1*. This approach is limited by the available data.

None of the acute, short-, intermediate- term, or chronic MOEs for ambient air exposure during the high-use season exceed HED's level of concern for 1,3-D (MOEs less than 30). Cancer risk for multiple sources (ambient air exposure) of 1,3-dichloropropene was estimated from monitoring data collected from over 20 sites over multiple years. These sites were in areas of high use and urban environments. The cancer risk estimates for all but one monitoring site, in a high use area, ranged from 2×10^{-6} to 9×10^{-8}, which are below the Agency's level of concern. The monitoring data for this site resulted in a risk estimate of 6×10^{-6}, which does exceed the Agency's level of concern. However, the data for this site in the following year was almost two orders of magnitude lower. Therefore, over a lifetime of exposure, the risk estimates would likely be below the level of concern. The results are summarized in Table 6.2.

Table 6.2 Results of 2000 Through 2001 California Ambient Monitoring In High Use Areas During Season Of Use

CA. County	Site	Dates & Mon. Days (N)	24 Hr. TWAs (ppm) Maximum	7-9 Week [1] (mean of means) (ppm)	Acute MOE[2]	Short-term MOE[3]	Interm-term MOE[3]	Chronic MOE[4]	Cancer Risk[5]
Kern	ARB	7/19 - 8/31/2000	0.00139	0.00021	54000	24000	980	1800	4.66e-07
		6/30 - 8/30/2001	0.00015	0.00004	504000	125000	5100	9200	8.88e-08
	SHA	7/19 - 8/31/2000	0.00089	0.00012	85000	42000	1700	3100	2.66e-07
	CRS	7/19 - 8/31/2000	0.02825	0.00293	2700	1700	70	130	6.50e-06
		6/30 - 8/30/2001	0.00060	0.00004	126000	125000	5100	9200	8.88e-08
	MVS	7/19 - 8/31/2000	0.00798	0.00039	9500	12800	530	950	8.66e-07
		6/30 - 8/30/2001	0.00164	0.00019	46000	26000	1100	1900	4.22e-07
	VSD	7/19 - 8/31/2000	0.00319	0.00035	24000	14000	600	1100	7.77e-07
		6/30 - 8/30/2001	0.00795	0.00044	9500	11000	460	840	9.76e-07
	MET	7/19 - 8/31/2000	0.00922	0.00056	8207	8900	370	660	1.24e-06
		6/30 - 8/30/2001	0.00300	0.00018	25000	28000	1100	2100	4.00e-07

Table 6.2 Results of 2000 Through 2001 California Ambient Monitoring In High Use Areas During Season Of Use

CA. County	Site	Dates & Mon. Days (N)	24 Hr. TWAs (ppm) Maximum	7-9 Week [1] (mean of means) (ppm)	Acute MOE[2]	Short-term MOE[3]	Interm-term MOE[3]	Chronic MOE[4]	Cancer Risk[5]
	ARV	6/30 - 8/30/2001	0.0211	0.00099	3600	5100	210	370	2.20e-06
Monterey and Santa Cruz	CHU	9/11 - 11/2/2000	0.00096	0.00009	79000	56000	2300	4100	2.00e-07
		9/8 - 11/7/2001	0.00040	0.00005	189000	100000	4100	7400	1.11e-07
	OAS	9/11 - 11/2/2000	0.00032	0.00004	236000	125000	5100	9200	8.88e-08
	SAL	9/11 - 11/2/2000	0.00008	0.00001	946000	500000	20500	36900	2.22e-08
		9/8 - 11/7/2001	0.00032	0.00005	236000	100000	4100	7400	1.11e-07
	LJE	9/11 - 11/2/2000	0.00007	0.00001	1081000	500000	20500	36900	2.22e-08
		9/8 - 11/7/2001	0.00108	0.00007	70100	71400	2900	5300	1.55e-07
	PMS	9/11 - 11/2/2000	0.00079	0.00006	96000	83000	3400	6200	1.33e-07
		9/8 - 11/7/2001	0.00092	0.00009	82200	56000	2300	4100	2.00e-07
	MES	9/8 - 11/7/2001	0.0047	0.00025	16100	20000	820	1500	5.55e-07
	SES	9/11 - 11/2/2000	0.00006	0.00001	1260000	500000	20500	36900	2.22e-08
		9/8 - 11/7/2001	0.00023	0.00004	329000	125000	5100	9200	8.88e-08

1 samples taken for 7 and 9 weeks for Kern County in 2000 and Kern County in 2001, respectively. Samples taken for 8 weeks in Monterey and Santa Cruz Counties in 2000 and 2001.
2 Acute MOE = HEC (75.67 ppm)/Maximum 24 hour TWA.
3 Short-,Intermediate-term = HEC (5.0 ppm, 0.205 ppm, and 0.182 ppm for short-, intermediate- and chronic, respectively)/7/8/9 week average.
4 Chronic MOE = HEC (0.182 ppm)/mean of weekly means. Chronic exposure is amortized for 180 days of exposure per year.
5 Cancer Risk = Q1*(1.8×10^{-2} ppm^{-1}) x LADE (mean of weekly means x 63 days exposure during study/365 days per year x 50 years/70 year lifetime).

6.2.2 Exposures from Urban Background Ambient Air Monitoring

In 2002, CARB added 1,3-D to its list of toxic air contaminants for which it routinely screens (see http://www.cdpr.ca.gov/docs/empm/pubs/tac/monitoring.htm).

The 2002 CARB monitoring sites are located throughout California in urban environments that included urban areas such as Long Beach, Burbank, Los Angeles, Fremont, Fresno, San Francisco and San Jose. The statistical summaries of the 2002/2003 CARB monitoring data are provided in Table 6.3.

(http://www.arb.ca.gov/adam/toxics/statepages/tdcpstate.html, and http://www.arb.ca.gov/adam/toxics/statepages/cdcpstate.html).

HED calculated acute, short- intermediate-term and chronic MOEs as well as cancer risk for urban background exposure to 1,3-D. None of the estimated MOEs or cancer risks exceeds HED's levels of concern. Acute risks (MOEs) were calculated by comparing the maximum 24 hour TWA to the acute HEC. The median is compared to the selected HECs to calculate short- and intermediate-term risk (MOEs).

Chronic MOEs are calculated by comparing the median to the chronic HEC. Since the Agency considers chronic exposures as those lasting for 180 days or longer, estimates of chronic exposure are amortized by 180 days of exposure per year. Chronic exposures (i.e., exposures at some level 6 months or so to every day over the course of a year) in and around most of the monitored urban sites probably do not occur. For the majority of sites, few residues were detected above the limit of detection (LOD). Based on these monitoring data, a chronic risk assessment is probably less germane than a short- or intermediate-term assessment because of the use patterns for 1,3-D. However, chronic exposure to urban background ambient air is assessed as an upper bound of exposure and is assumed to present a conservative assessment of risk.

HED calculates cancer risk based on an estimate of lifetime average daily exposure. To represent the average exposure an individual may receive over a lifetime, the lifetime average daily exposure (LADE) is calculated using the mean or average daily exposure. The LADE is then multiplied by the non-occupational Q_1* to determine cancer risk. HED amortized the average daily exposure by 180 days based on the assumption assumed that individuals may be exposed to average urban background air concentrations chronically (i.e., 180 days per year), for 50 years. As described above, since the likelihood of chronic exposure is expected to be low, this assessment is considered conservative.

Table 6.3 Results of 2002 & 2003 California Ambient Monitoring In Urban Areas

Site	Year	N	Results of Annual 1,3 Dichloropropene (ppm)[1]					MOEs				Cancer Risk[6]
			Min	Median	Mean[2]	90th %tile	Max	acute-term[3]	short-term[4]	interm-term[4]	chronic[5]	
Statewide	2003	503	0.0001	0.0001	0.0001	0.0001	0.0014	54000	50000	2100	3700	6.3e-07
	2002	440	0.0001	0.0001	0.0001	0.0001	0.0009	84100	50000	2100	3700	6.3e-07
Azusa	2003	28	0.0001	0.0001	0.0001	0.0001	0.0001	757000	50000	2100	3700	6.3e-07
	2002	27	0.0001	0.0001	0.0001	0.001	0.0001	757000	50000	2100	3700	6.3e-07
Burbank	2003	26	0.0001	0.0001	--	0.0001	0.0001	757000	--	--	3700	6.3e-07
	2002	30	0.0001	0.0001	0.0001	0.0001	0.0001	757000	50000	2100	3700	6.3e-07
Calexico	2003	30	0.0001	0.0001	0.00014	0.00025	0.0004	189200	35714	1500	3700	6.3e-07
	2002	29	0.0001	0.0001	0.00015	0.0001	0.0009	84100	33333	1400	3700	6.3e-07
Chula Vista	2003	28	0.0001	0.0001	--	0.0001	0.0001	757000	--	--	3700	6.3e-07
	2002	29	0.0001	0.0001	0.0001	0.0001	0.0001	757000	50000	2100	3700	6.3e-07
El Cajon	2003	30	0.0001	0.0001	0.0001	0.0001	0.0001	757000	50000	2100	3700	6.3e-07
	2002	28	0.0001	0.0001	0.0001	0.0001	0.0001	757000	50000	2100	3700	6.3e-07
Los Angeles	2003	29	0.0001	0.0001	0.0001	0.0001	0.0001	757000	50000	2100	3700	6.3e-07
	2002	21	0.0001	0.0001	--	0.0001	0.0001	757000	--	--	3700	6.3e-07
Long Beach	2003	27	0.0001	0.0001	0.0001	0.0001	0.0001	757000	50000	2100	3700	6.3e-07
	2002	25	0.0001	0.0001	0.0001	0.0001	0.0001	757000	50000	2100	3700	6.3e-07
Riverside	2003	30	0.0001	0.0001	0.0001	0.0001	0.0001	757000	50000	2100	3700	6.3e-07
	2002	25	0.0001	0.0001	--	0.0001	0.0001	757000	--	--	3700	6.3e-07
Simi Valley	2003	31	0.0001	0.0001	0.0001	0.0001	0.00015	504500	50000	2100	3700	6.3e-07
	2002	26	0.0001	0.0001	0.0001	0.0001	0.0001	757000	50000	2100	3700	6.3e-07
Bakersfield	2003	29	0.0001	0.0001	0.10006	0.0001	0.0014	54100	31250	1300	3700	6.3e-07
	2002	29	0.0001	0.0001	0.00014	0.00025	0.0005	151000	35714	1500	3700	6.3e-07
Chico	2003	31	0.0001	0.0001	0.0001	0.0001	0.0001	757000	50000	2100	3700	6.3e-07

Table 6.3 Results of 2002 & 2003 California Ambient Monitoring In Urban Areas												
Site	Year	N	Results of Annual 1,3 Dichloropropene (ppm)[1]					MOEs				Cancer Risk[6]
			Min	Median	Mean[2]	90th %tile	Max	acute-term[3]	short-term[4]	interm-term[4]	chronic[5]	
	2002	29	0.0001	0.0001	0.0001	0.0001	0.0001	757000	50000	2100	3700	6.3e-07
Fremont	2003	30	0.0001	0.0001	0.0001	0.0001	0.0001	757000	50000	2100	3700	6.3e-07
	2002	27	0.0001	0.0001	0.0001	0.0001	0.0001	757000	50000	2100	3700	6.3e-07
Fresno	2003	31	0.0001	0.0001	0.00011	0.0001	0.0005	151000	45455	1900	3700	6.3e-07
	2002	30	0.0001	0.0001	0.00011	0.0001	0.0006	126000	45455	1900	3700	6.3e-07
Roseville	2003	31	0.0001	0.0001	0.0001	0.0001	0.0001	757000	50000	2100	3700	6.3e-07
	2002	29	0.0001	0.0001	0.0001	0.0001	0.0001	757000	50000	2100	3700	6.3e-07
San Francisco	2003	31	0.0001	0.0001	0.0001	0.0001	0.0001	757000	50000	2100	3700	6.3e-07
	2002	15	0.0001	0.0001	--	0.0001	0.0001	757000	--	--	3700	6.3e-07
San Jose - 4th Street	2003	0	--	--	--	--	--	--	--	--	--	--
	2002	8	0.0001	--	--	--	0.0001	757000	--	--	--	--
San Jose - Jackson St.	2003	31	0.0001	0.0001	0.0001	0.0001	0.0001	757000	50000	2100	3700	6.3e-07
	2002	6	0.0001	--	--	--	0.0001	757000	--	--	--	--
Stockton	2003	30	0.0001	0.0001	0.0001	0.0001	0.00025	303000	50000	2100	3700	6.3e-07
	2002	27	0.0001	0.0001	0.0001	0.0001	0.0003	252000	50000	2100	3700	6.3e-07
Mexicali – Mexico	2003	17	0.0001	0.0001	--	0.0001	0.0001	757000	--	--	3700	6.3e-07
	2002	19	0.0001	0.0001	--	0.0001	0.0001	757000	--	--	3700	6.3e-07
Rosarito – Mexico	2003	30	0.0001	0.0001	0.0001	0.0001	0.0001	757000	50000	2100	3700	6.3e-07
	2002	25	0.0001	0.0001	--	0.0001	0.0001	757000	--	--	3700	6.3e-07

[1] Concentrations were derived by summing the concentrations of cis and trans 1,3-D. 0.0002 LOD = 0.0001 cis 1,3-D + 0.0001 trans 1,3-D. Values below LOD assumed to be ½ LOD.
[2] Means shown only for years with data in all 12 months.
[3] Acute MOE = HEC (75.67 ppm)/maximum air concentration value.
[4] Short- and Intermediate-term MOE = HEC (5.0 ppm for short-term and 0.205 ppm for intermediate-term)/mean air concentration value.
[5] Chronic MOE = HEC (0.182 ppm)/median air concentration value. Chronic exposure is amortized for 180 days of exposure per year.
[6] Cancer Risk = $Q_1^*(1.8 \times 10^{-2}\ ppm^{-1})$ x LADE (median air concentration value x 180 days of exposure/365 days per year x 50 years/70 year lifetime).

7.0 Aggregate Risk Assessment

In accordance with the FQPA, HED must consider and aggregate pesticide exposures and risks from three major sources: food, drinking water, and residential exposures. In an aggregate assessment, exposures from relevant sources are added together and compared to quantitative estimates of hazard (e.g., a NOAEL or PAD), or the risks themselves can be aggregated. When aggregating exposures and risks from various sources, HED considers both the route and duration of exposure.

7.1 Acute Aggregate Risk

No dietary acute endpoints were identified, so the only acute exposures quantitatively assessed were the bystander inhalation exposures. The bystander assessments for inhalation exposures are presented in sections 6.1 and 6.2.

7.2 Short-Term and Intermediate-Term Aggregate Risk

As previously discussed in section 3.5.9, the toxicity endpoints for inhalation and dietary exposures are different, so it would be inappropriate to aggregate exposures from these pathways. The bystander assessments for inhalation exposures are presented in sections 6.1 and 6.2. The aggregated dietary risk for food and water exposures is discussed in section 5.2.

7.3 Long-Term Aggregate Risk

As previously discussed in section 3.5.9, the toxicity endpoints for inhalation and dietary exposures are different, so it would be inappropriate to aggregate exposures from these pathways. The bystander assessments for inhalation exposures are presented in section 6.2. The aggregate dietary risk assessment for food and water exposures is discussed in section 5.2.2. The combined exposure is less than the level of concern, with the combined food and drinking water (from ground water sources) at less than 1% of the PAD for all populations, and the combined food and drinking water (from surface water sources) at less than 5% of the PAD for all populations.

7.4 Cancer Aggregate Risk

As previously discussed in section 3.5.9, the tumors identified in the carcinogenicity studies from for inhalation and dietary studies are different, so it would be inappropriate to aggregate exposures from these pathways for the cancer assessment. The bystander cancer assessments for inhalation exposures are presented in Section 6.2.

The aggregated food and water assessment is discussed in section 5.2.3. These risks represent upper bound risks for a person living in agricultural area(s) where 1,3-D is used extensively or where a person obtains drinking water from an aquifer that led directly from an area where 1,3-D is used. HED is generally concerned when cancer risks exceed 1×10^{-6}. Because of the uncertainties regarding estimation of cancer potency and human exposure, risk estimates ranging from 1 to 3×10^{-6} are generally considered indistinguishable. The results of the cancer dietary risk analyses are presented in Table 5.4. The estimated cancer risk for food alone and food and drinking water from groundwater sources is below HED's level of concern for 1,3-D and its degradates.

Although risk for drinking water from surface water sources for 1,3-D exceeds the negligible standard, based on characterization of the model estimates provided by EFED, HED considers the risk estimates to be an overestimate, and likely to be similar those of ground water sources. As discussed in Section 5.1.8, the surface water model, PRZM-EXAMS is not designed for chemicals such as 1,3-D where volatilization is the primary route of dissipation. Insufficient data are available to further refine the inputs to the model, leading to the assumption of much slower degradation in the environment by the model than is likely. The limited surface water monitoring data available for high use areas did not show any detects of 1,3-D and its degradates.

Historically, EFED's concern about exposure to 1,3-D in drinking water has been from ground water exposure sources. This is due to very high application rates (hundreds of pounds per acre) for the existing pre-plant fumigation uses, and its high mobility in soil (and thus potential to leach to ground water). Once introduced into ground water, 1,3-D is shielded from many of the processes that can contribute to its more rapid dissipation from surface water. These include photolysis, volatilization to the atmosphere from the surface of water bodies, volatilization due to the motion of flowing water (both during run-off and stream flow), and the greater availability of

oxygen for biological metabolism. All of these processes combined make it likely that exposure from surface water sources will be less than that from ground water sources (Eckel 2008). Because the cancer risk from ground water sources is below the Agency's level of concern without the benefit of these processes to aid dissipation, HED believes that the cancer risk from surface water sources will also be below the Agency's level of concern based on its likely dissipation from surface water sources.

Cancer risk for multiple sources (ambient air exposure) of 1,3-dichloropropene was estimated from monitoring data collected from over 20 sites over multiple years. These sites were in areas of high use and urban environments. The cancer risk estimates for all but one monitoring site, in a high use area, ranged from 2×10^{-6} to 9×10^{-8}, which are below the Agency's level of concern. The monitoring data for this site resulted in a risk estimate of 6×10^{-6}, which does exceed the Agency's level of concern. However, the data for this site in the following year was almost two orders of magnitude lower. Therefore, over a lifetime of exposure, the risk estimates would likely be below the level of concern. In more populated urban environments air concentrations were below the analytical limit of detection in 21 of 28 site/year combinations considered. In the remaining, values were measured but did not result in cancer risks of concern. Therefore, the Agency does not have a concern for the cancer risk from 1,3-dichloropropene.

8.0 Cumulative Risk Assessment and Characterization

Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding as to 1,3-D and any other substances and 1,3-D does not appear to produce a toxic metabolite produced by other substances. For the purposes of this reregistration action, therefore, EPA has not assumed that 1,3-D has a common mechanism of toxicity with other substances. For information regarding EPA's efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see the policy statements released by EPA's Office of Pesticide Programs concerning common mechanism determinations and procedures for cumulating effects from substances found to have a common mechanism on EPA's website at http://www.epa.gov/pesticides/cumulative/.

9.0 Occupational Exposures

This section of the risk assessment focuses on potential exposures and risk to occupational handlers, to occupational reentry workers who could be exposed when entering 1,3-D-treated areas to perform crop-production tasks, and to occupational bystanders who could be exposed when performing crop-production tasks near (but not inside) 1,3-D-treated areas. This assessment describes the occupational exposures for the proposed new use only. The occupational assessment for the existing uses may be found in the most recent risk assessment associated with the RED (Vogel, 2007).

Since the majority of 1,3-D is used seasonally with typical applications lasting 2 weeks, 1 to 2 times per year, it is expected that the majority of worker exposure will be acute and short-term in duration. Due to model limitations, the PERFUM model was only used to calculate post-

application exposure for the acute durations. Monitoring data were used to calculate post-application acute, short-term and cancer risk (see Appendix E). However, there is potential for use by commercial applicators as well as private growers. Since commercial applicators may apply 1,3-D to many fields over the course of the use season, they are expected to have a longer durations of exposure than private growers. Therefore, acute, short- and intermediate-term exposures are assessed for commercial mixer, loaders, and applicators of 1,3-D (see Section 9.0 of the Phase 5 RED).

It should be noted that the RfC methodology used to calculate inhalation risk incorporates an adjustment for expected duration of exposure. It is presumed that exposure occurs during the course of an average work week (8 hours of work per day and 5 days per week). For this reason, the worker assessment is considered conservative for both private growers and commercial applicators.

Since 1,3-D is formulated as a liquid there is some potential for dermal and eye contact. The use of mitigation controls such as personal protective equipment (PPE) and closed transfer systems (as required on the Cordon™ label) minimizes the potential but does not eliminate it. Although 1,3-D may be irritating to the skin and eyes, no dermal endpoints of concern were selected for risk assessment purposes. However, the high vapor pressure of 1,3-D also makes quantifying any potential low level exposures very difficult. Therefore, a quantitative dermal exposure assessment has not been completed.

9.1 Post-plant Drip Irrigation Fumigations

Mixer/Loader/Applicator Exposure

The registrant has proposed a post-plant drip irrigation use of 1,3-D in established vineyards. HED has no new data for worker exposure resulting specifically from the post-plant drip irrigation application of 1,3-D. However, mixing and loading techniques for the proposed use are expected to be similar to loading techniques assessed for the existing agricultural uses of 1,3-D. Specifically, exposure for bulk and mini-bulk loading methods were assessed in the most recent RED. No data are available to assess drip irrigation applicator exposure; however, since this type application is closed system, exposure is expected to be negligible.

As noted above, bulk and mini-bulk loading exposure was evaluated in the Phase 5 RED for 1,3-D. The data evaluated in the recent RED is the only data available to assess exposure for loading of 1,3-D. It should be noted that the study data used to estimate bulk and mini-bulk loader exposure are based on a much higher application rate than the proposed application rate for the post-plant vineyard use. For this reason, loader exposure for the proposed post-plant use is expected to be significantly lower than that assessed for bulk and mini-bulk loading for the existing pre-plant uses of 1,3-D.

Exerted from the Phase 5 RED:
As a result of the March 1992 Data Call-In (DCI), DowElanco submitted final reports of worker air monitoring studies conducted in 1992 and 1993 at the Moses Lakes, Washington, Buckeye, Arizona, and Hookerton, North Carolina (MRID 42946201, 42845602). These studies monitored loaders, applicators and workers involved in

drum and bulk loading and related applications of various 1,3-D products. Studies were conducted in accordance with product label directions and utilizing regional commercial application techniques associated with application of Telone II and Telone C-17. As a result of the Special Review negotiations between DowElanco and EPA, drum loading of 1,3-D products was phased out in late 1996. A delivery method known as mini-bulk was promoted as replacement for drum loading. Subsequently, Dow submitted a study conducted in Ainger, North Carolina, in which mini-bulk cylinder were used (MRID 43880401). These three studies were evaluated in the 1998 1,3-D RED to determine exposure and risk for workers involved in 1,3-D loading and applications.

For the loaders and applicators, two kinds of samples were collected: four hour samples, and task-specific short duration (4 to 46 minutes) samples. The four hour samples provided inherently time- weighted average air concentrations over a major fraction of a work day, while the task-specific samples measured the air concentrations associated only with high-contact activities. For product loaders, these activities were the actual loading events. The 4-hour loader samples included the loading events, and the time spent on site between loading events. In the most recent Ainger, NC worker monitoring study, only short-term task specific samples were collected. Sampling occurred only when workers were actively engaged in loading. Because the number of monitored replicates at each site was small, HED pooled the results from different sites, to obtain the largest possible sample sizes for each exposure scenario. Details of the worker monitoring studies are described in detail in the 1998 RED.

Data evaluated in the 1998 RED was not modified. The air concentration values are the same as those used in Table 7 of the 1998 RED document. However, in the 1998 RED, estimates for commercial handlers and private growers were presented separately, assuming that private grower will perform both loading and application and spend most of their work day engaged in application rather than loading. Exposures estimates for growers were based on the air concentration for application rather than loading. Estimates of exposure for commercial loaders and applicators were presented separately, assuming 5 to10 hours per work day.

The current document provides assessments of commercial loader and applicator exposure only, for each task monitored (as listed in Table 7 of the 1998 RED document). Since commercial applicators may apply 1,3-D to many fields over the course of the use season, they are expected to have a more exposure than private growers. To support this assumption, HED used estimates of daily and yearly work hours as supplied by the Agency's Biological and Economic Analysis Division (BEAD). BEAD determined that the Total Lifetime Work Hours were 500 hours for private farmers/growers (5 hrs/day x 10 days/year x 10 years/lifetime) and 3200 hours for commercial handlers (8 hrs/day x 20 days/year x 20 years/lifetime). HED used BEAD's assessment of lifetime work hours for commercial handlers (8 hrs/day x 20 days/year x 20 years/lifetime) as the basis for the current assessment. Since the estimate lifetime work hours for commercial handlers are greater than that of the private growers, the current worker assessment is considered conservative for both private growers and commercial applicators.

Acute risks (MOEs) are calculated by comparing the maximum air concentration level of 1,3-D at an individual sample point to the toxicological human equivalent concentration (HEC) selected for acute exposures. To calculate the short-and intermediate-term risks to handlers, the mean air concentration level of 1,3-D are calculated across all sites for each different handler task and method of application. This mean air concentration levels are compared to the HEC selected for short- and intermediate-term. Cancer risk is calculated by multiplying the LADE by the occupational Q_1. The LADE used for cancer risk assessment assumes 20 days of exposure per year for 20 years per lifetime.*

Table 14 summarizes the risks for loading activities and applicators involved in pre-plant broadcast and row applications. Overall, the data indicate that risks exceed HED's level of concern for workers involved in 1,3-D loading and application when no respiratory protection is used. OV respirators, which reduce exposure levels by a factor of 10, are also considered and reduce exposure do not exceed HED's level of concern for most workers involved in 1,3-D application with these devices. However, even with the use of OV respirators, which are required on current 1,3-D labels, the intermediate-term MOEs for bulk loading exceed HED's LOC (LOC is for MOEs less than 30). It is likely that the risk estimates for bulk loading is conservative because this assessment assumes that this activity is done over the course of a normal work week, 8 hours per day, 5 days per week. The available monitoring study indicates that actual loading activities comprise a small part of the entire work day (approximately 15 minutes to 1 hour). However, since this assessment is for commercial applicators and BEAD information indicates that commercial applicators can work for 8 hours /day, HED will use these current inputs until data are

available to support refinements to ensure HED does not underestimated risk. Data which indicated the division of work for commercial applicators (i.e., time spent loading and time spent applying) could be used to refine the bulk loading risk estimates. Note that if bulk loading only occurs for one hour (or less) per day, the intermediate-term bulk loading risk would not exceed the LOC.

Table 14: 1,3-D Air Concentrations Monitoring Data for Agricultural Workers as listed in the 1998 RED

Activity	*Sample Duration*	*Study Site*	*Total reps*	*Max*	*Air Concentration (ppm)*		*MOE*			*Cancer Risk[3]*
					Mean	*Median*	*acute[1]*	*Short[2]*	*interm[2]*	
Bulk Loading[a]	*4 hrs*	*WA, AZ*	*10*	*1.29*	*0.35*	*0.14*	*176.35*	*42.38*	***2.43 (24.3)[4]***	***1.2E-04*** *(1.2E-05)[4]*
Bulk Loading[a]	*task only*	*WA, AZ*	*10*	*7.05*	*2.35*	*1.05*	*32.20*	***6.38*** *(64)[4]*	***0.37 (4)*** *[4]*	***6.6E-04*** *(6.6E-05)[4]*
Mini-bulk Loading[a]	*task only*	*NC*	*12*	*0.26*	*0.10*	*0.10*	*886.51*	*148.98*	***8.54*** *(85.4)[4]*	*2.4E-05* *(2.4E-06)[4]*
Bulk, Mini-bulk, and Drum Application[b]	*4 hrs & task*	*WA, AZ, NC*	*28*	*1.43*	*0.29*	*0.25*	*158.96*	*50.86*	***2.92 (29.2)[4]***	***1.34E-04*** *(1.3E-05)[4]*

a With use of dry disconnects
b With use of end-row spill control
1 Acute MOE = HEC (227 ppm)/maximum air concentration value.
2 Short- and Intermediate-term MOE = HEC (15 ppm for short-term and 0.86 ppm for intermediate-term)/mean air concentration value.
3 Cancer Risk = Q1(1.8 x 10^{-2} ppm) x (8 hours/24 hours -) x LADE (median air concentration value x 20 days/365 days per year x 20 years/70 year lifetime).*
4 () = addition of OV respirator.

Occupational Bystander Exposure

One field volatility study is available to address post-application exposure from this use (MRID 45296101). Using this field volatility study, modeling is done for the post-plant drip irrigation using the PERFUMS model. The resulting buffer distances were estimated to be zero (see section 6.1 for details). However, the Agency has some concerns with the quality of this study. First, the application rate used in the study was 5.4 lbs ai/acre, while the maximum application rate allowable is 17.74 lbs ai/acre. In general, the Agency believes that scaling down from the maximum application rate is acceptable, assuming a linear relationship between application rate and flux rate. However, the Agency has concerns with the practice of scaling up flux rates to the maximum application rate, as it is unclear if soil saturation may occur that causes more off-gassing (flux) than expected. Additionally, while flux rates were calculated from this study data, the regression analysis for most periods yielded poor r-squared values and reordering of the data was required. This is a standard practice, but a better designed study probably would have yielded better results. A smaller field and samplers placed closer to the edges of the field (e.g., the samplers in this study were roughly 300 ft away whereas most studies have samplers

approximately 30 ft away) would have produced a higher quality of data. As a result, the Agency has low confidence in the flux rates obtained from this study.

However, since the risk estimates for the 1,3-D pre-plant drip agricultural uses (all of which are applied at much higher application rates) are not of concern at 0 meters from treated fields, the Agency expects that the post-plant vineyard use will not pose a risk of concern for bystanders. Since the current flux study is considered minimally adequate to model exposure, the Agency recommends that a new field volatility study be conducted to confirm the conclusions reached with the currently post-plant drip irrigation study (MRID # 452961-01). The confirmatory study should be conducted at the maximum label rate of 17.4 lbs ai/Acre and should have samplers placed closer to the treated field (approximately 30 feet). Since the available post-plant study only monitored air concentrations of 1,3-D at 300 feet from the treated field, HED recommends that the Cordon™ label require a buffer distance of 300 feet until the requested confirmatory field volatility data for this use are received and reviewed.

The Agency has limited data (i.e, one field volatility study) to assess the post-plant drip irrigations use. However, the Agency has additional field volatility data for the existing pre-plant drip irrigation use of 1,3-D, which is very similar to the proposed post-plant drip irrigation use. To further characterize the potential risks resulting from the proposed use, the HED has provided a summary of risk results for the pre-plant irrigation uses. This assessment indicates low concern for occupational bystander exposure resulting from the existing drip irrigation uses. Additionally, it should be noted that the proposed post-plant drip irrigation uses are applied at significantly lower application rates than the existing pre-plant drip irrigation uses. For this reason, exposure and risk related to the proposed use is expected to be significantly lower than that of the pre-plant drip irrigation uses (presented below).

Exerted from the Phase 5 RED: Pre-plant Drip Irrigation Applications: *HED has no data for worker exposure resulting from the drip irrigation application of 1,3-D. However, there are field volatility data available to address off-site exposure from this use. The ISCST3 Model is used to estimate occupational bystander exposures following/during a single pre-plant drip irrigation application of 1,3-D to outdoor agricultural fields. The model allows HED to examine the effect of several variables, including field size, emission ratios, wind speed, and atmospheric stability. Air concentration levels estimated by the ISCST3 Model are based on the assumption that occupational bystanders would be exposed during an eight-hour work day. [Details of the ISCST3 analysis are available in Appendix C.]. Table 17 shows the acute risks (MOEs) estimated by comparing the toxicological human equivalent concentration of concern to the estimated air concentration levels. Generally, risks do not exceed HED's level of concern ((LOC is for MOEs less than 30). Although the ISCST3 model assessment is considered be a high-end estimate of actual exposure, HED does not have data to refine the current assessment.*

As noted above, the modeling analysis done for the existing pre-plant drip irrigation use indicates that there is low concern for acute occupational bystander exposure resulting from 1,3-D application. However, field volatility studies for 1,3-D indicate that peak emissions from treated fields occur up to 72 hours after application. At this time, the models cannot readily be used to evaluate exposures of longer duration. When appropriate distributional models are available, short-term, intermediate-term and cancer risk may be reassessed with models that can better estimate longer term, average exposures (e.g., a SOFEA© analysis based on existing uses).

Table 17. ISCST3 MOEs At Selected Distances Downwind For Occupational Exposure to Pre-Plant Agricultural Field Fumigations, Telone EC												
App. Meth.	ER (%)	Fld Size (A)	DW Dist. (M)	Differing Meteorological Conditions									
				1 m/s 2.3 mph	1.4 m/s 3.1 mph	1.8 m/s 4 mph	2.2 m/s 5 mph	2.7 m/s 6 mph	3.1 m/s 7 mph	3.6 m/s 8 mph	4.0 m/s 9 mph	4.5 m/s 10 mph	4.5 m/s 10 mph
				Stab D	Stab C	Stab C	Stab C	Stab C	Stab C	Stab C	Stab C	Stab C	Stab B
Drip Irrigation, Raised Bed, Untarped	7.8	1	25	105	228	293	359	441	505	588	650	732	1040
			100	238	565	727	889	1083	1253	1444	1600	1825	3059
			500	1316	4727	6118	7429	8667	10400	11556	13000	14857	34667
		5	25	67	148	190	233	286	328	381	423	477	675
			100	130	296	381	466	571	658	765	846	954	1405
			500	406	1253	1600	1962	2419	2737	3250	3586	4000	8667
		10	25	57	126	162	198	243	279	324	360	405	575
			100	102	235	302	370	454	520	605	671	754	1106
			500	279	782	1010	1238	1507	1733	2000	2261	2537	5200
		20	25	49	109	140	171	210	241	280	310	350	498
			100	82	190	245	299	366	421	488	545	612	889
			500	203	536	689	839	1030	1182	1368	1529	1733	3250
		40	25	42	95	122	149	183	211	244	272	305	439
			100	67	157	202	246	302	348	403	448	505	743
			500	153	395	507	619	759	874	1020	1130	1268	2261
Drip Irrigation, Raised Bed, Tarped	2.2	1	25	375	813	1051	1284	1576	1793	2080	2311	2600	3714
			100	852	2000	2600	3152	3852	4522	5200	5778	6500	10400
			500	4727	17333	20800	26000	34667	34667	52000	52000	52000	104000
		5	25	241	531	680	832	1020	1169	1368	1507	1705	2419
			100	462	1061	1368	1651	2039	2364	2737	3059	3355	4952
			500	1444	4522	5778	6933	8667	9455	11556	13000	14857	34667

Table 17. ISCST3 MOEs At Selected Distances Downwind For Occupational Exposure to Pre-Plant Agricultural Field Fumigations, Telone EC												
App. Meth.	ER (%)	Fld Size (A)	DW Dist. (M)	Differing Meteorological Conditions									
				1 m/s 2.3 mph	1.4 m/s 3.1 mph	1.8 m/s 4 mph	2.2 m/s 5 mph	2.7 m/s 6 mph	3.1 m/s 7 mph	3.6 m/s 8 mph	4.0 m/s 9 mph	4.5 m/s 10 mph	4.5 m/s 10 mph
				Stab D	Stab C	Stab C	Stab C	Stab C	Stab C	Stab C	Stab C	Stab C	Stab B
		10	25	203	450	578	707	867	1000	1156	1284	1444	2039
			100	365	839	1083	1316	1625	1857	2167	2419	2667	4000
			500	1000	2811	3586	4333	5474	6118	7429	8000	8667	17333
		20	25	174	388	500	612	748	860	1000	1106	1253	1793
			100	294	680	874	1072	1316	1507	1733	1926	2167	3152
			500	727	1926	2476	2971	3714	4160	4952	5474	6118	11556
		40	25	151	340	437	533	654	754	874	972	1095	1576
			100	240	562	722	881	1083	1238	1444	1600	1793	2667
			500	545	1405	1825	2213	2737	3152	3586	4000	4522	8000

10.0 Data Needs and Label Requirements

10.1 Toxicology

No additional studies are required at this time.

10.2 Residue Chemistry

The following confirmatory studies are needed to support an unconditional registration.

860.1340 Residue Analytical Methods
An independent laboratory validation is required for the tolerance enforcement method that determines the 3-chloroacrylic acid and 3-chloroallyl alcohol metabolites.

OPPTS Guideline 860.1360 Multiresidue Methods
Multiresidue method data are required for 1,3-dichloropropene and its 3-chloroacrylic acid and 3-chloroallyl alcohol metabolites.

OPPTS Guideline 860.1380 Storage Stability
A storage stability study demonstrating stability of 1,3-dichloropropene and its 3-chloroacrylic acid and 3-chloroallyl alcohol metabolites in grapes for at least 154 days is required.

10.3 Occupational and Residential Exposure

No additional studies are required at this time.

11.0 References

Abel, S., 6/26/00; D260209 and D260210 (Environmental Fate Assessment).

Eckel, W., 1/18/08, *Characterization of the Drinking Water Assessment for Telone*.

Olinger, C.; 5/24/2007; DP D318734; *Amended Registration for Grapes: Summary of Analytical Chemistry and Residue Data*.

Olinger, C.; 6/13/07; DP D340060; *Amended Registration for Grapes: Summary of Analytical Chemistry and Residue Data*.

Olinger, C.; 12/14/07; DP Barcode: D346778; *Follow-up on Proposed New Use for Drip Irrigation in Vineyards: Drinking Water and Residential Assessments*.

Vogel, D. *et al;* 4/12/2007; DP D337328; *1,3-Dichloropropene: HED Human Health Risk Assessment for Phase 5*.

Appendix A: Executive Summaries for Critical Studies and Toxicological Profile

Acute Inhalation Exposure

Critical Studies: Acute Inhalation Studies - Rats

EXECUTIVE SUMMARY: In one acute inhalation study (MRID No.4022093), Wistar rats were exposed to Telone II at 454, 647, 699, 762, 832 or 958 ppm for 4 hours (whole body exposure). The mortality rates were as follows: 0, 20, 30, 50, 100 and 100% at 454, 647, 699, 762, 832 and 958 ppm dose levels, respectively. In a second study (MRID 41672201), Fischer 344 rats were exposed to cis- 1, 3 dichloropropene at 0, 583, 771, or 1020 ppm for 4 hours (whole body exposure). No animals died at 583 ppm; however, body weight loss (13% decrease in body weight) during days 2 through 7 was seen in rats exposed to this concentration. Rats regained their weight on day 8. At 1020 ppm, all exposed animals died immediately following the exposure and 771 ppm exposed animals died during the 14 day observation period. **Accordingly, 454 ppm or an HEC of 75.67 ppm** (non-occupational risk assessment) or **227.0 ppm** (occupational risk assessment) **was selected as the NOAEL based on decreased body weights at the LOAEL of 583 ppm.**

Short-term Inhalation Exposure

Critical Study: Developmental Toxicity Study - Rabbits

EXECUTIVE SUMMARY : In a developmental toxicity study (MRID 001444715 and 00152848), New Zealand rabbits (17-24 females/group) were exposed to aerosol concentrations of 1,3-D (90.1%) at 0, 20, 60 or 120 ppm (equivalent to approximately 0, 0.091, 0.272 or 0.545 mg/L) 6 hours/day during gestation days 6 through 18. **The maternal NOAEL was 20 ppm (0.091 mg/L). The maternal LOAEL was 60 ppm (0.272 mg/L) based on decreased body weight gains compared with controls.** The developmental NOAEL was 120 ppm (0.545 mg/L). The developmental LOAEL was >120 ppm (> 0.545 mg/L, HDT). No Telone II related malformations were reported.

Intermediate-term Inhalation Exposure

Critical Study: 13-Week Inhalation Toxicity Study - Rats

EXECUTIVE SUMMARY: In a subchronic (13-week) toxicity study (MRID 00146461) Fischer 344 rats (10 sex/group) were exposed to concentrations of Telone II at 0, 10, 30, 90 or 150 ppm, 6 hours/day, 5 days/week for 13 weeks. Both sexes of rats at 90 and 150 ppm exhibited a significant decreases in body weights while rats at 30, 60 and 150 ppm exhibited treatment-related histopathological lesions in the nasal turbinates. **The NOAEL was 10 ppm (0.045 mg/L) and the LOAEL was 30 ppm (0.136 mg/L), based on histopathological lesions in the nasal turbinates.**

Long-term Inhalation Exposure

Critical Study: Chronic toxicity/carcinogenicity study - Mice

EXECUTIVE SUMMARY: In a chronic toxicity/carcinogenicity study (MRID 40312301), B6C3F1 mice (50/sex/group plus 10/sex/group to 6- and 12-month exposure groups) were exposed by whole-body inhalation to Telone II (92.1%) at aerosol concentrations of 0, 5, 20 or 60 ppm (equivalent to approximately 0, 0.023, 0.091 or 0.272 mg/L) 6 hours/day, 5 days/week for a total of 510 days over a two-year period. There was no effect on survival (at least 80% in each group). There was a statistically significant decrease in body weight gain in 60 ppm males (3-9%) and females (2-11%). Urinary bladder effects were noted primarily in females at 20 and 60 ppm (slight, moderate or marked roughened, irregular and opaque surfaces were reported in 20/50 at 20 ppm and 30/49 at 60 ppm compared with 3/50 slight in the control group). Hypertrophy and hyperplasia of the nasal respiratory mucosa (very slight/slight) were observed in most 60 ppm mice of both sexes and in 20 ppm females. Degeneration of olfactory epithelium (very slight/slight) was noted in most 60 ppm mice of both sexes. Hyperplasia of the epithelial lining of the nonglandular portion of the stomach was observed in 60 ppm males (0, 5, 20 and 60 ppm: males = 0, 3, 1 and 8; females = 0, 0, 0 and 2). For chronic toxicity, the NOEL was 5 ppm (0.023 mg/L) and the LOEL was 20 ppm (0.091 mg/L) based on urinary bladder hyperplasia and hypertrophy/hyperplasia of the nasal respiratory mucosa. Hyperplasia of the epithelial lining of the nonglandular portion of the stomach was observed in a higher incidence compared with controls in 60 ppm males and, to a lesser extent, 60 ppm females. There was evidence of carcinogenicity. Bronchioloalveolar adenomas appeared in a higher incidence in 60 ppm males only compared with controls (0, 5, 20 and 60 ppm = 9/50, 6/50, 13/50 and 22/50). Although the lung tumors noted in the mouse inhalation study were benign, tumor induction was dose dependent, tumor incidence was outside the range of historical controls and the tumor type was also seen in the mouse oral bioassay.

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 (Memo from Kerry Dearfield to Herman Toma, Second Peer Review of Telone II, dated December 8, 1989). 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.

Chronic Oral Exposure

Critical Study: Combined Chronic Toxicity/Carcinogenicity Study in Rats

EXECUTIVE SUMMARY: In a chronic toxicity/carcinogenicity study (MRID 43763501), Telone II (96% a.i.) was administered as microcapsules by dietary admix to Fischer 344 rats (60/sex/group with 10/sex/group sacrificed at 12 months) at levels of 0, 2.5, 12.5 or 25 mg/kg/day for two years. Body weight gains were decreased for males (8 and 21%) and females (15 and 25%) at 12.5 and 25 mg/kg/day compared to controls. Food consumption was decreased in females at 25 mg/kg/day. There was an increase in liver masses/nodules in males only at 12.5 and 25 mg/kg/day. There was an increased incidence of basal cell hyperplasia of the nonglandular mucosa of the stomach of both sexes at the 12- and 24-month sacrifices at 12.5 and 25 mg/kg/day. For chronic toxicity, the NOEL was 2.5 mg/kg/day and the LOEL was 12.5 mg/kg/day based on a decrease in body weight gain compared with controls and an increase in the incidence of basal cell hyperplasia of the nonglandular mucosa of the stomach. There was evidence of carcinogenicity. The incidences of rats with primary hepatocellular adenomas were as follows respectively (0, 2.5, 12.5 or 25 mg/kg/day): males = 2/50, 1/50, 6/50 and 9/50; females = 0/50, 0/50, 0/50 and 4/50. These data indicate that exposure to Telone II increases the incidence of these tumors in males at the two highest doses and in females at the highest dose. The highest dose tested in this study (25 mg/kg/day) was considered adequate to assess the carcinogenic potential of 1,3-D in rats.

Discussion of Tumor Data: The incidences of rats with primary hepatocellular adenomas were as follows respectively (0, 2.5, 12.5 or 25 mg/kg/day): males = 2/50, 1/50, 6/50 and 9/50; females = 0/50, 0/50, 0/50 and 4/50. These data indicate that exposure to Telone II increases the incidence of these tumors in males at the two highest doses and in females at the highest dose.

EXECUTIVE SUMMARY: In a study reported by the National Toxicology Program (NTP) in 1985 (MRID 0014669), 1,3-D (89.0% a.i.) was administered in corn oil (with 1.0% epichlorohydrin as a stabilizer) by gavage to Fischer 344 rats (52/sex/group) at doses of 0, 25 or 50 mg/kg/day three times per week for 104 weeks. A total of 77 rats per sex was used for each dose group, including those sacrificed for examination during the course of testing. Basal cell or epithelial hyperplasia of the forestomach was reported. The NTP concluded that there was "clear evidence of carcinogenicity" for males and "some evidence of carcinogenicity" for females.

Discussion of Tumor Data: Statistically significant increases in the incidence of the following tumors were observed in the highest dose tested (HDT) by pairwise comparison with controls:

1) forestomach squamous cell papillomas in males and females;
2) combined forestomach squamous cell papillomas and carcinomas combined in males; and
3) liver neoplastic nodules in males and combined neoplastic nodules and hepatocellular carcinomas in males.

The increased incidence of forestomach tumors was accompanied by a statistically significant positive trend for forestomach basal cell hyperplasia in male and female rats of both treatment

groups (25 and 50 mg/kg). There were also positive trends for other tumors in rats (*i.e.*, in females, mammary gland adenomas or fibromas and thyroid gland follicular cell adenomas or carcinomas; in males, adrenal gland pheochromocytomas). The highest dose tested in rats (50 mg/kg) appeared to be adequate for carcinogenicity testing.

In 1992, the registrant conducted a second feeding study using timed-released (microencapsulated) doses of 1,3-D in food since the stomach tumors seen in the NTP study coincided with the area where the feeding tube was inserted. In addition, the NTP study results may have been confounded by the presence of a stabilizer, epichlorohydrin, which is a known carcinogen.

In a chronic toxicity/carcinogenicity study (MRID No. 43763501), Telone II (96% a.i.) was administered as microcapsules by dietary admix to Fischer 344 rats (60/sex/group with 10/sex/group sacrificed at 12 months) at levels of 0, 2.5, 12.5 or 25 mg/kg/day for two years.

Body weight gains were decreased for males (8 and 21%) and females (15 and 25%) ar 12.5 and 25 mg/kg/day compared to controls. Food consumption was decreased in females at 25 mg/kg/day. There was an increase in liver masses /nodules in males only at 12.5 and 25 mg/kg/day. There was an increased incidence of basal cell hyperplasia of the nonglandular mucosa of the stomach of both sexes at the 12- and 24-month sacrifices at 12.5 and 25 mg/kg/day. For chronic toxicity, the NOAEL was 2.5 mg/kg/day and the LOAEL was 12.5 mg/kg/day based on a decrease in body weight gain compared with controls and an increase in the incidence of basal cell hyperplasia of the nonglandular mucosa of the stomach. There was evidence of carcinogenicity.

Discussion of Tumor Data: The incidences of rats with primary hepatocellular adenomas were as follows respectively (0, 2.5, 12.5 or 25 mg/kg/day): males = 2/50, 1/50, 6/50 and 9/50; females = 0/50, 0/50, 0/50 and 4/50. These data indicate that exposure to 1,3-D increases the incidence of these tumors in males at the two highest doses and in females at the highest dose. The highest dose tested in this study (25 mg/kg/day) was considered adequate to assess the carcinogenic potential of 1,3-D in rats.

Critical Study: Combined Chronic Toxicity/Carcinogenicity Study in Mice

EXECUTIVE SUMMARY: In a study with B6C3F1 mice (50/sex/group) reported by the NTP in 1985 (MAID 00146469), Telone II (89.0 % a.i.) was administered in corn oil (with 1.0% epichlorohydrin) by gavage at doses of 0, 25 or 50 mg/kg/day three times per week for 104 weeks. The study in males was not considered to be adequate because of the mortality of controls at weeks 48-51(25/50, myocarditis) and the 104-week survival for males (8/50, 28/50 and 31/50). Squamous cell papillomas of the forestomach (0/50, 1/50 and 2/50 for females), squamous cell carcinomas of the forestomach (0/50, 0/50 and 2/50 for females), transitional cell carcinomas of the urinary bladder 0/50, 8/50 and 21/48 for females) and alveolar/bronchiolar adenomas (0/50, 3/50 and 8/50 for females) were seen. In males, the study was considered to be inadequate for carcinogenicity (due to mortality of controls). For females, there was clear evidence of carcinogenicity".

Discussion of Tumor Data: A statistically elevated incidence of the following tumors was observed at either HDT or a both dose levels:

1) forestomach squamous cell papillomas or papillomas and carcinomas combined in males and females, and squamous cell carcinomas in females;
2) urinary bladder transitional cell carcinomas in males and females;
3) lung adenomas or adenomas and carcinomas combined in males and females.

Several deficiencies were noted in the mouse study, including excessive mortality in control males and inadequate randomization procedures at the study initiation. The highest dose tested appears to have been excessive. While this study was not used for quantitatively estimating 1,3-D's carcinogenic potential, the Agency has included the stomach, bladder and lung effects in its weight-of-the-evidence findings.

Toxicity Profile

Guideline No./ Study Type	MRID No./ Classification /Doses	Results
Subchronic Toxicity Studies*		
870.3100 90-Day oral toxicity rodents [Fischer 344 rats]	42954802 Acceptable/guideline 0, 5, 15, 50 or 100mg/kg/day in diet	NOAEL = 5 mg/kg/day LOAEL = 15 mg/kg/day based on hyperkeratosis and/ or basal cell hyperplasia in the non-glandular portion of the stomach (both sexes)
870.3100 90-Day oral toxicity rodents [B6C3F1 mice]	42954801 Acceptable/guideline 0,15, 50, 100 or 175 mg/kg/day in diet	NOAEL = 15 mg/kg/day LOAEL = 50 mg/kg/day based on decreased body weights and body weight gain (both sexes)
870.3100 90-Day oral toxicity nonrodent	See 870.4100b, below	
870.3465 30-Day inhalation toxicity rodent [Fischer 344 rats]	00039685 Acceptable/guideline 0, 3, 10 or 30 ppm (0, 0.0136, 0.045 or 0.136 mg/L) 6 hours/day, 5 days/week	NOAEL = 30 ppm (0.136 mg/L), highest dose tested LOAEL = >30 ppm
870.3465 30-Day inhalation toxicity rodent [CD-1 mice]	00039685 Acceptable/guideline 0, 3, 10 or 30 ppm (0, 0.0136, 0.045 or 0.136 mg/L) 6 hours/day, 5 days/week	NOAEL = 30 ppm (0.045 mg/L), highest dose tested LOAEL = >30 ppm (0.136 mg/L)
870.3465 90-Day inhalation toxicity rodent [Fischer 344 rats]	00146461 Acceptable/guideline 0, 10, 30, 90 or 150 ppm (0, 0.045, 0.136, 0.408,or 0.680 mg/L) 6 hours/day, 5 days/week	NOAEL = 10 ppm (0.045 mg/L) LOAEL = 30 ppm (0.136 mg/L) based on histopathological lesions in the nasal turbinates
870.3465 30-Day inhalation toxicity rodent [B6C3F1 mice]	00146461 Acceptable/guideline 0, 10, 30, 90 or 150 ppm (0, 0.045, 0.136, 0.408,or 0.680 mg/L) 6 hours/day, 5 days/week	NOAEL = 10 ppm (0.045 mg/L) LOAEL = 30 ppm (0.136 mg/L) based on histopathological lesions in the nasal turbinates
Developmental and Reproductive Toxicity Studies*		

Guideline No./ Study Type	MRID No./ Classification /Doses	Results
870.3700a Prenatal developmental in rodents [Fischer 344 rats]	00144715, 00152848 Acceptable/guideline 0, 20, 60 or 120 ppm (0, 0.091, 0.272 or 0.545 mg/L) by inhalation 6 hours/day during gestation days 6 through 15	Maternal NOAEL = <20 ppm (0.091 mg/L) LOAEL = 20 ppm (0.091 mg/L) based on decreased body weight gain and food consumption Developmental NOAEL <120 ppm (0545 mg/L), highest concentration tested LOAEL =120 ppm (0545 mg/L) based on increased delay in ossification of the vertebral centra
870.3700b Prenatal developmental in nonrodents [New Zealand White Rabbit]	00144715, 00152848 Acceptable/guideline 0, 20, 60 or 120 ppm (0, 0.091, 0.272 or 0.545 mg/L) by inhalation 6 hours/day during gestation days 6 through 18	Maternal NOAEL = 20 ppm (0.091 mg/L) LOAEL = 60 ppm (0.272 mg/L) based on decreased body weight gain Developmental NOAEL 120 ppm (0545 mg/L), highest concentration tested LOAEL >120 ppm (0545 mg/L)
870.3800 Reproduction and fertility effects [Fischer 344 rats]	40312401, 40835301 Acceptable/guideline 0, 10, 30 or 90 ppm (0, 0.045, 0.136, or 0.408 mg/L) by inhalation 6 hours/day, 5 days/week (premating) 6 hours/day, 7 days/week (F_0 breeding at weeks 11-13, during gestation and lactation; F_{1a} and F_{1b}, dams from gestation day 20 until postpartum day 5; F_1 ♂♀ parents after weaning and continued for 12 weeks, 5 days/week	Parental/Systemic NOAEL = 30 ppm (0.136 mg/L) LOAEL = 90 ppm (0.408 mg/L) based on decreased body weight gain, microscopic non-glandular stomach lesions and hyperplasia of the nasal respiratory epithelium with focal degeneration of the olfactory tissue Reproductive NOAEL = 90 ppm (0.408 mg/L), highest concentration tested LOAEL >90 ppm (0.408 mg/L) Offspring NOAEL = 90 ppm (0.408 mg/L), highest concentration tested LOAEL >90 ppm
Chronic Toxicity Studies*		
870.4100b Chronic toxicity nonrodent [Beagle dog]	42441001 Acceptable/guideline 0, 0.5, 2.5 or 15 mg/kg/day microcapsules by **dietary** admix	NOAEL = 2.5 mg/kg/day LOAEL = 15 mg/kg/day based on decreased body weight gain, microcytic anemia, an increase in hematopoietic activity in both sexes and possible increased liver weights in males
870.4300 Combined Chronic Oral Toxicity/Carcino-genicity for 2 year rat study [Fischer 344 rats]	43763501 Acceptable/guideline 0, 2.5, 12.5 or 25 mg/kg/day microcapsules by **dietary** admix	Chronic Toxicity NOAEL = 2.5 mg/kg/day LOAEL = 12.5 mg/kg/day based on decreased body weight gain and an increase in the incidence of basal cell hyperplasia of the non-glandular mucosa of the stomach Carcinogenicity: Increased incidence of rats with primary hepatocellular adenomas: 0, 2.5, 12.5 and 25 mg/kg/day = ♂ 2/50, 1/50, 6/50 and 9/50; ♀ 0/50, 0/50, 0/50 and 4/50
870.4300 Combined Chronic Toxicity/Carcinogenici ty (104 week)	00146469, NTP study Acceptable/guideline 0, 25 or 50 mg/kg/day by **oral gavage** 3 times/week	Chronic Toxicity NOAEL = not established LOAEL = 25 mg/kg/day based on increased tumor incidence Carcinogenicity: Increased incidence of squamous cell papillomas of the forestomach: 0, 25 and 50 mg/kg/day = ♂

Guideline No./ Study Type	MRID No./ Classification /Doses	Results
[Fischer 344 rats]	for 104 weeks	1/52, 1/52 and 9/52; ♀ 0/52, 2/52, 3/52. Squamous cell carcinomas: ♂ 0/52, 0/52 and 4/52. Neoplastic nodules of the liver: ♂ 1/52, 6/52 and 7/52: ♀ 6/52, 6/52, 10/52. NTP concluded that there was "clear evidence of carcinogenicity" in males and "some evidence" of carcinogenicity in females
870.4300 Combined Chronic Toxicity/Carcino-genicity (104 week)[B6C3F1 mice]	43757901 Acceptable/guideline 0, 2.5, 25 or 50 mg/kg/day microcapsules by **dietary** admix	Chronic toxicity NOAEL = 2.5 mg/kg/day LOAEL = 25 mg/kg/day based on lower body weights and decreased body weight gain (both sexes) Carcinogenicity: No evidence of carcinogenicity but study not adequate for assessment due to several deficiencies in conduct.
870.4300 Combined Chronic Toxicity/Carcino-genicity (104 week)[B6C3F1 mice]	00146469, NTP study Acceptable/guideline 0, 25 or 50 mg/kg/day by **oral gavage** 3 times/week for 104 weeks	Chronic Toxicity NOAEL = not established LOAEL = 25 mg/kg/day based on increased mortality in males Carcinogenicity: Increased incidence of squamous cell papillomas of the forestomach: 0, 25 and 50 mg/kg/day = ♀ 0/50, 1/50, 2/50. Squamous cell carcinomas of thee forestomach: ♀ 0/50, 0/50, 2/50. Transitional cell carcinomas of the urinary bladder: ♀ 0/50, 8/50, 21/50. Alveolar/bronchiolar adenomas: ♀ 0/50, 3/50, 8/50. In ♂, study was inadequate for carcinogenicity. NTP concluded that there was "clear evidence of carcinogenicity" in females
870.4300 Combined Chronic Toxicity/Carcino-genicity (2 years) [Fischer 344 rats]	40312201 Acceptable/guideline 0, 5, 20 or 60 ppm (0, 0.023, 0.091 or 0.272 mg/L) by **inhalation** 6 hours/day, 5 days /week for 509 days	Chronic Toxicity NOAEL = 20 ppm (0.091 mg/L) LOAEL = 60 ppm (0.272 mg/L) based on histopathological changes in nasal tissue (males and females) and a suggestion of decreased body weight gain (first year of the study only) There was no evidence of carcinogenicity
870.4300 Combined Chronic Toxicity/Carcino-genicity (2 years) [B6C3F1 mice]	40312301 Acceptable/guideline 0, 5, 20 or 60 ppm (0, 0.023, 0.091 or 0.272 mg/L) by **inhalation** 6 hours/day, 5 days /week for 510 days	Chronic Toxicity NOAEL = 5 ppm (0.023 mg/L) LOAEL = 20 ppm (0.091 mg/L) based urinary bladder hyperplasia, and hypertrophy/hyperplasia of the nasal respiratory mucosa Carcinogenicity: Increased incidence of bronchioloalveolar adenomas: 0, 5, 20 or 60 ppm = ♂ 9/50, 6/50, 13/50 or 22/50. Although the lung tumors were benign, tumor induction was concentration dependent, the tumor incidence was dose dependent, the tumor incidence was outside of the historical controls, and the tumor type was seen in the mouse oral bioassay.
Genotoxicity Studies		
Gene Mutation 870.5300 *In vitro* mammalian cell in culture gene	47020332 Acceptable/guideline 50-250 µM -S9 50-200 µM +S9	Negative up to cytotoxicity (≥200 µM -S9) or the highest dose tested +S9

Guideline No./ Study Type	MRID No./ Classification /Doses	Results
mutation assay Chinese hamster ovary (CHO) cells		
Gene Mutation 870.5300 *Drosophila melanogaster* sex-linked recessive lethal mutations	00146469 (1985) Acceptable/guideline 0, 5750 ppm/feeding	Positive: Induction of sex-linked recessive lethal mutations but negative for the induction of reciprocal translocations at 5750 ppm National Toxicology Program (NTP); Valencia *et al.*, Environ Mutagenesis 7:325-348.
Gene Mutation 870.5300 Host Mediated assay	00039688 Acceptable/guideline 0, 30, 60 mg/kg (oral gavage administration at 1, 2 & 3 hrs)	Negative up to the highest dose tested
Cytogenetics 870.5375 *In vitro* mammalian cytogenetics assay CHO cells	NTP (1989) Acceptable/Guideline 4.91-49.1 µg/mL -S9 (Trial 1) 50-100 µg/mL -S9 (Trial 2) 10-50 µg/mL +S9 (Trial 1 only)	Negative up to concentrations causing 50% reduction in cell confluency (≥50 µg/mL ± S9)NTP: Loveday *et al.*, Environ Mutagenesis 13:6–94.
Cytogenetics 870.5395 *In vivo* mouse micronucleus assay	259101 (1985) Acceptable/guideline 0, 38, 115, 380 mg/kg	Negative up to a lethal dose (380 mg/kg)
Cytogenetics 870.5450 Dominant Lethal Mutation in Sprague Dawley Rats	44302801 (1997) Acceptable/guideline 0-150 ppm, 7 da/wk, 10 wks (whole body inhation)	Negative up to the LOAEL of 150 ppm, based on adverse effects on body weight.
Other Effects 870.5500 Bacterial DNA repair *Bacillus subtilis* H15 & M45	00039688 (1978) Acceptable/guideline 50-1,250 µg/well	Positive: Preferential inhibition of the DNA repair deficient strain at 1250 µg/well
Other Effects 870.5550 Unscheduled DNA Synthesis Primary rat hepatocytes	00146467(1985) Acceptable/guideline $3x10^{-3}$ to $1x\ 10^{-6}$M	Negative up to a cytotoxic level (3×10^{-4} M)
Other Effects 870.5900 *In vitro* sister chromatid exchange(SCE) CHO cells	NTP (1989) Acceptable/Guideline 0.995-29.900 µg/mL -S9 (Trial 1) 30-50 µg/mL -S9 (Trial 2) 2.990-29.900 µg/mL +S9	Positive: Significant and concentration-related ↑in SCE induction at 30-50 µg/mL -S9 & 10 -30 µg/mL +S9. These levels were not cytotoxic.

Guideline No./ Study Type	MRID No./ Classification /Doses	Results
	(Trial 1 only)	
METABOLITES OF 1,3-DICHLOROPROPENE		
Gene Mutation 870.5100 *In vitro* bacterial reverse gene mutation assay *Salmonella typhimurium* TA98, TA100, TA1535, TA1537 *Escherichia coli* WP2 *(uvrA)*	44940327 (1999) 3-Chloroacrylic acid Acceptable/guideline 500 - 5000 µg/plate ±S9	Negative in independently performed preincubation assays up to the limit concentration
Gene Mutation 870.5100 *In vitro* bacterial reverse gene mutation assay *Salmonella typhimurium* TA98, TA100, TA1535, TA1537 *Escherichia coli* WP2 *(uvrA)*	44940326 (1999) 3-Chloroallyl alcohol Acceptable/guideline 33.3 - 5000 µg/plate ±S9	Negative in independently performed preincubation assays up to the limit concentration
Gene Mutation 870.5300 *In vitro* mammalian cell in culture gene mutation assay mouse lymphoma L5178Y	44940311 (1999) 3-Chloroallyl alcohol Acceptable/guideline Trial 1:12.5- 925 µg/mL -S9; 1.5-100 µg/mL +S9 Trial 2:12.5- 500 µg/mL -S9; 3-100 µg/mL +S9	Positive: Dose-related and reproducible ↑ MF at 400 and 500 µg/mL -S9 & 75 and 100 µg/mL +S9: no difference in the induction of small or large mutant colonies
Cytogenetics 870.5395 *In vivo* mouse (CD-1) micronucleus assay	44940312 (1999) 3-Chloroacrylic acid Acceptable/guideline 62.5-250 mg/kg (♂) 62.5-200 mg/kg (♀)	Negative up to overtly toxic (death and/or decreased activity) highest doses
MECHANISM STUDIES		
Gene Mutation *In vitro* bacterial reverse gene mutation assay *Salmonella typhimurium* TA100 plus mouse lung homogenate	44460501 Unacceptable /non-guideline 100-450 µg/plate - metabolic activation; 150-1000 µg/plate + untreated mouse lung homogenate -glutathione (GSH)or 75-1000 µg/plate +GSH; 75-1000 µg/plate ± GSH + mouse lung S9 (pretreated with 63 ppm	Negative at any concentration ± GSH and ± untreated or 1,3-D lung S9 but under conditions that would not favor a mutagenic response -S9 (no epoxidized soybean stabilizer, purification through silicic column and storage at 5°C under N_2) or +S9 because of low level microsomal/oxidative proteins in the lung preparation

Guideline No./ Study Type	MRID No./ Classification /Doses	Results
	1,3-D, 5da/wk, 2.5 wks)	
Gene Mutation *In vivo* with transgenic Big Blue B6C3F1 mice gene mutation assay target gene *(lacI*)	44470501 Unacceptable /non-guideline 0, 10, 60, 150 ppm (via whole body inhalation) 6 hrs/da, 5 da/wk, 2 wks	Negative in lung and liver tissue but test system uncertainties weaken the understanding of the negative response.
Other Mutagenic Effects *In vitro* DNA binding assays	44446301 Unacceptable /non-guideline 11 mM reacted w calf thymus DNA ± S9 (Aroclor 1254-induced rat liver) ± GSH	Inconclusive -S9; negative +S9 ± GSH but uncertainties regarding use of optimum conditions
Mechanism of Tumorigenicity ♂B6C3F1 mice & ♂ Fischer 344 rats	44446302 Unacceptable /non-guideline 0, 5,12.5, 25, 100 mg/kg (oral gavage-rats) 3, 12 26 days 0, 10, 30, 60, 150 ppm (whole body inhalation-mice) 6 hrs/da, 5 da/wk, 2 wks	RATS:. No mortality or clinical signs S ↓GSH at 25 & 100 mg/kg (adaptive process) but liver tumors were seen in the 2-yr bioassay at 12.5 mg/kg. No conclusion possible for apoptosis or cell proliferation because of variability in data. No conclusion possible for DNA adduct formation because of variability in data & small sample size. MICE: No mortality or clinical signs. Data show conjugation of 1,3-D w GSH in lung tissue, no clear effect on cell proliferation or apoptosis in bronchiole epithelium or bladder transitional cells or DNA adduct formation in lungs but extreme variability and small sample size compromised the findings. Concerns regarding whether a biological effective dose was achieved.
GSH Activity in Several Mammalian Cell Lines: ♂B6C3F1 mice & ♂ Fischer 344 rats primary rat hepatocytes, CHO cells, Chinese hamster lung cells, *Salmonella typhimurium*	44460503 Unacceptable /non-guideline GSH measurements in cell lines reacted with various substrates: ^{13}C-1,3-D; 4-chloro-1,3-dinitrobenzene; para-nitro-phenylethylbromide; trans-4-phenyl-3-buten-2-one	No conclusions relative to the correlation between physiological levels of GSH and mitigation of mutagenicity Low level GSH activity with S. typhimuruim but conflicting results with various mammalian cell lines (*i.e.*, high & low level GSH activity with cell lines producing negative mutagenicity data and high GSH activity with 2 cell lines that were positive in standard mutagenicity assays)
Bioavailabity of Microencapsulated Telone II in Female Rats	44460502 Unacceptable /non-guideline Phase I: 25 mg/kg ^{13}C-1,3D coadministered w 25 mg/kg microencap-sulated 1,3-D sampled at 1,3,5,10,15, 20, 30,40,50,or 60 min. Phase II: 25 or 50 mg/kg ^{13}C-1,3D + microencap-sulated 1,3-D; 25 or 50 mg/kg ^{13}C-1,3D + 7.5 or 15	No conclusions because of unclear study design, technical deficiencies and biased treatment of the data.

Guideline No./ Study Type	MRID No./ Classification /Doses	Results
	mg/kg microencap-sulated 1,3-D	
Initiation-Promotion: Mechanism of Mouse Lung Tumors ♂A/J mice	45897502B&D Unacceptable /non-guideline 16 mg/kg vinyl carbamate(VC) (initiator) ± 0, 60 ppm 1,3-D (whole body inhalation 6 hrs/da, 5 da/wk, 25 wks)	Lung adenomas in 1,3-D alone 26% vs 10% in air control suggest initiating event. Lack of ↑total tumors for VC-treated alone vs. VC + 1.3-D does not support a promoter role for 1,3-D
Initiation-Promotion: Mechanism of Rat Liver Tumors ♂ Fischer 344 rats	45897502C&D Unacceptable /non-guideline 100 mg/kg diethylnitrosamine (DEN, initiator) + 0, 25 mg/kg/da 1,3-D; 80 mg/kg phenobarbital (PB, promoter); or 5-10 mg/kg 2-acetylaminofluorene (2-AAF, complete carcinogen)	Data do not support a promotional role for 1,3-D.

Appendix B: Methodologies for Inhalation Risk Calculations
1,3-Dichloropropene (Telone II) Array

METHODOLOGIES FOR INHALATION RISK CALCULATIONS

In evaluating the risks that a compound may pose to human health after exposure *via* the inhalation route, different methodologies have been historically used by the USEPA and the California Department of Pesticide Regulation (CDPR). The Agency's approach to calculating risks due to inhalation exposure is based on the

guidance methodology developed by the Office of Research and Development (ORD) for the derivation of inhalation reference concentrations (RfCs) and human equivalent concentrations (HECs) for use in margin of exposure (MOE) calculations (RfC methodology). The two approaches differ in their use of species-specific parameters to derive HECs. Therefore, the differences noted in the risk assessments of each organization are due, in part, to their use of different methodologies and use of different uncertainty factors (UFs). The Agency's approach to calculating risks due to inhalation exposure is based on the guidance methodology developed by the Office of Research and Development (ORD) for the derivation of inhalation reference concentrations (RfCs) and human equivalent concentrations (HECs) for use in margin of exposure (MOE) calculations (RfC methodology). An example of CDPR's methodology, and the species-specific parameters used in this approach can be found in the CDPR website and their 1,3-D risk assessment, Appendix G at the following web address: www.cdpr.ca.gov/docs/dprdocs/methbrom/append_g.pdf. As OPP understands the importance to harmonize, to the extent possible, with other regulatory agencies, this risk assessment will present HECs derived using both methodologies.

The RfC methodology applies a dosimetric adjustment that takes into consideration not only the differences in ventilation rate (MV) but also the physicochemical properties of the inhaled compound, the type of toxicity observed (*e.g.* systemic vs. port of entry) and the pharmacokinetic (PK) **but not pharmacodynamic** (PD) differences between animals and humans.

Based on the RfC guidance (1994), the methodology for RfCs derivation is an estimate of the quantitative dose-response assessment of chronic non-cancer toxicity for individual inhaled chemicals and includes dosimetric adjustment to account for the species-specific relationships of exposure concentration to deposited/delivered dose. This adjustment is influenced by the physicochemical properties of the inhaled compound as well as the type of toxicity observed (*e.g.* systemic vs. port of entry), and takes into consideration the PK differences between animals and humans. Though the RfC methodology was developed to estimate toxicity of inhaled chemicals over a lifetime, it can be used for other inhalation exposures (*e.g.* acute and short-term exposures) since the dosimetric adjustment incorporates mechanistic determinants of disposition that can be applied to shorter duration of exposures provided the assumptions underlying the methodology are still valid. These assumptions, in turn, vary depending on the type of toxicity observed and will be discussed later on in this document. Thus the derivation of a HEC for inhaled gases is described by the following equation:

$$HEC = POD_{study} * \frac{D_{animal\ exposure\ (hrs\ /\ day)}}{D_{human\ exposure\ (hrs\ /\ day)}} * \frac{W_{animal\ exposure\ (days\ /\ wk)}}{W_{human\ exposure\ (days\ /\ wk)}} * RGDR$$

Where:

POD_{study}: Point of departure identified in the critical toxicology study
$D_{animal\ exposure}$: Duration of animal exposure (hrs/day; days/wk)
$D_{anticipated\ exposure}$: Anticipated human duration of exposure (hrs/day; days/wk)
RGDR: Regional Gas Dose Ratio

For gases eliciting both port of entry and systemic effects, calculations to estimate the inhalation risk to humans are dependent on the regional gas dose ratio (RGDR). In the case of systemic effects, the RGDR is defined as the ratio of the blood:gas partition coefficient of the chemical for the test species to humans ($H_{b/g\ animal}/H_{b/g\ human}$). When this ratio is unknown or when the $H_{b/g\ animal} > H_{b/g\ human}$ a default value of 1.0 is used as the RGDR. This default is based on the observation that for chemicals where partition coefficient data are available in both rats and humans the RGDR value has usually been comparable or slightly higher than 1. Thus, the use of an RGDR of 1 results in a protective calculation of the inhalation risk. Some of the key assumptions fundamental to the use of the RfC methodology to derive a HEC based on systemic effects include:

1) all the concentrations of inhaled gas within the animal's body are periodic with respect to time (*i.e.* periodic steady state - the concentration *vs* time profile is the same for every week). Periodicity must be attained for at least 90% of the exposure.
2) in the respiratory tract, the air, tissue, capillary blood concentration are in equilibrium with respect to each other.
3)systemically, the blood and tissue concentrations are in equilibrium with respect to each other.

In the case of 1,3-Dichloropropene, the physicochemical properties and metabolism data for the compound indicate that these conditions (*i.e.* periodicity and equilibrium between different compartments) will be achieved in a very short period of time. Under these conditions, therefore, the use of the RfC methodology to estimate acute inhalation risk is appropriate.

When the critical toxic effect in a study occurs in the respiratory tract (*i.e* port of entry effects), the RGDR is not related to the blood:gas partition coefficient of the compound but rather the ratio of the minute volume (MV) to the surface area (SA) of the affected region. In these instances, attaining periodicity or equilibrium between the compartments is not critical (since the effect is a function of the direct interaction between the inhaled compound and the affected region in the respiratory tract) and the RGDR may be calculated using the following equation:

$$RGDR = \frac{MV_{animal} / SA_{animal}}{MV_{human} / SA_{human}}$$

Where:
MV_{animal}: Minute volume for the test species (varies depending on body weight)
SA_{animal}: Surface area of the affected region in animals
MV_{human}: Minute volume for humans (default value is 13.8 l/min)
SA_{human}: Surface area of the affected region in humans

The MV_{animal} is calculated using the allometric scaling provided in USEPA (1988a). The equation for calculation of the MV_{animal} is:

$$\ln MV_{animal} = b_0 + b_1 \ln(BW)$$

Where:
ln MV_{animal} : natural logarithm of the minute volume
b_0 : species specific intercept used in the algorithm to calculate minute volumes based on body weight
b_1: species specific coefficient used in the algorithm to calculate minute volumes based on body weight
ln BW: natural logarithm of the body weight (expressed in kg)

The values for the species-specific parameters used to calculate the MV_{animal} based on body weight and the values for the surface areas of various regions of the respiratory tract (extrathoracic, thoracic, and pulmonary) are provided in the EPA document "Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry" (1994).

The magnitude of the UFs applied is dependent on the methodology used to calculate risk. When using the methodology developed by CDPR, a 100X UF is applied (10X for interspecies extrapolation and 10X for intraspecies variation). In contrast, the RfC methodology takes into consideration the PK differences **but not the PD differences**. Consequently, the UF for interspecies extrapolation may be reduced to 3X (to account for the PD differences) while the UF for intraspecies variation is retained at 10X. Thus, the UF when using the RfC methodology is customarily 30X.

The HED Arrays for 1,3-D may be found on the following pages.

HEC Array for Non-Occupational Risk Assessments¶												
Relevant Study		**LOAEL (ppm)**	**NOAEL (ppm)**	**Da**	**Dh**	**Wa**	**Wh**	**RGDR***	**HEC (ppm)**	**inter**	**Intra**	**UF**
Acute												
Acute Inhalation Study - RAT		**454**	**Not identified**	**4**	**24**	**1**	**1**	**1**	**75.67**	**3**	**10**	**1**
Short Term												
Dominant Lethal Study - Rats	Systemic	60	10	6	24	7	7	1	2.50	3	10	1
Initiation/Promotion Mechanistic Study Mice	Systemic	60	Not identified	6	24	5	7	1	10.71	3	10	3‡
30-Day Inhalation Mice		Not identified	30	6	24	5	7	1	5.36	3	10	1
30-Day Inhalation Rat		Not identified	30	6	24	5	7	1	5.36	3	10	1
Devel Rat	Maternal Systemic	20	Not identified	6	24	7	7	1	5.0	3	10	3‡
	Developmental	120	60	6	24	7	7	1	15	3	10	1
Dev Rabbit	**Maternal Systemic**	**60**	**20**	**6**	**24**	**7**	**7**	**1**	**5.0**	**3**	**10**	**1**
	Developmental	Not identified	120	6	24	7	7	1	30.0	3	10	1
Intermediate Term												
Dominant Lethal Study - Rats		60	10	6	24	7	7	1	2.50	3	10	1
Initiation/Promotion Mechanistic Study Mice	Systemic	60	Not identified	6	24	5	7	1	10.71	3	10	3‡
13-Week Inhalation Mouse	Local	30	10	6	24	5	7	0.157	0.282	3	10	1
13-Week Inhalation Rat	**Local**	**30**	**10**	**6**	**24**	**5**	**7**	**0.115**	**0.205**	**3**	**10**	**1**
Long-term												
Chronic Oncogenicity Rat	Systemic	60	20	6	24	5	7	1	3.57	3	10	1

HEC Array for Non-Occupational Risk Assessments[¶]												
Relevant Study		**LOAEL (ppm)**	**NOAEL (ppm)**	**Da**	**Dh**	**Wa**	**Wh**	**RGDR***	**HEC (ppm)**	**inter**	**Intra**	**UF**
	Local	60	20	6	24	5	7	0.204	0.73	3	10	1
Chronic Oncogenicity Mouse	Systemic	20	5	6	24	5	7	1	0.89	3	10	1
	Local	**20**	**5**	**6**	**24**	**5**	**7**	**0.204**	**0.182**	**3**	**10**	**1**
MultiGen Repro: Rat[§]	Parental Systemic	90	30	6	24	7	7	1	7.50	3	10	1
	Parental Local	90	30	6	24	7	7	0.204	1.53	3	10	1
Cancer Risk												
Chronic Oncogenicity Mouse	Bronchioalveolar adenomas (♂)	60	20	6	24	5	7	3.21	11.46	$Q_1^* = 4 \times 10^{-4}$ µg/m^3		

[¶] Bolded studies used for endpoint selection
[‡] 3X UF for LOAEL to NOAEL extrapolation is being recommended due to the mild nature of effects (decreased body weight) noted at the LOAEL
* Input parameters for the derivation of RGDRs were obtained from "Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry" (USEPA, 1994) Tables 4-4, 4-5, and 4-6.

Key for Array Table
LOAEL: Lowest observed adverse effect level
NOAEL: No observed adverse effect level
Da: Daily animal exposure (hrs/day)
Dh: Anticipated daily human exposure (hrs/day)
Wa: Weekly animal exposure (days/week)
Wh: Anticipated weekly human exposure (days/week)
RGDR: Regional Gas Dose Ratio
HEC: Human Equivalent Concentration
inter: interspecies extrapolation uncertainty factor
intra: intraspecies variation uncertainty factor
UF: Other uncertainty factor(s)

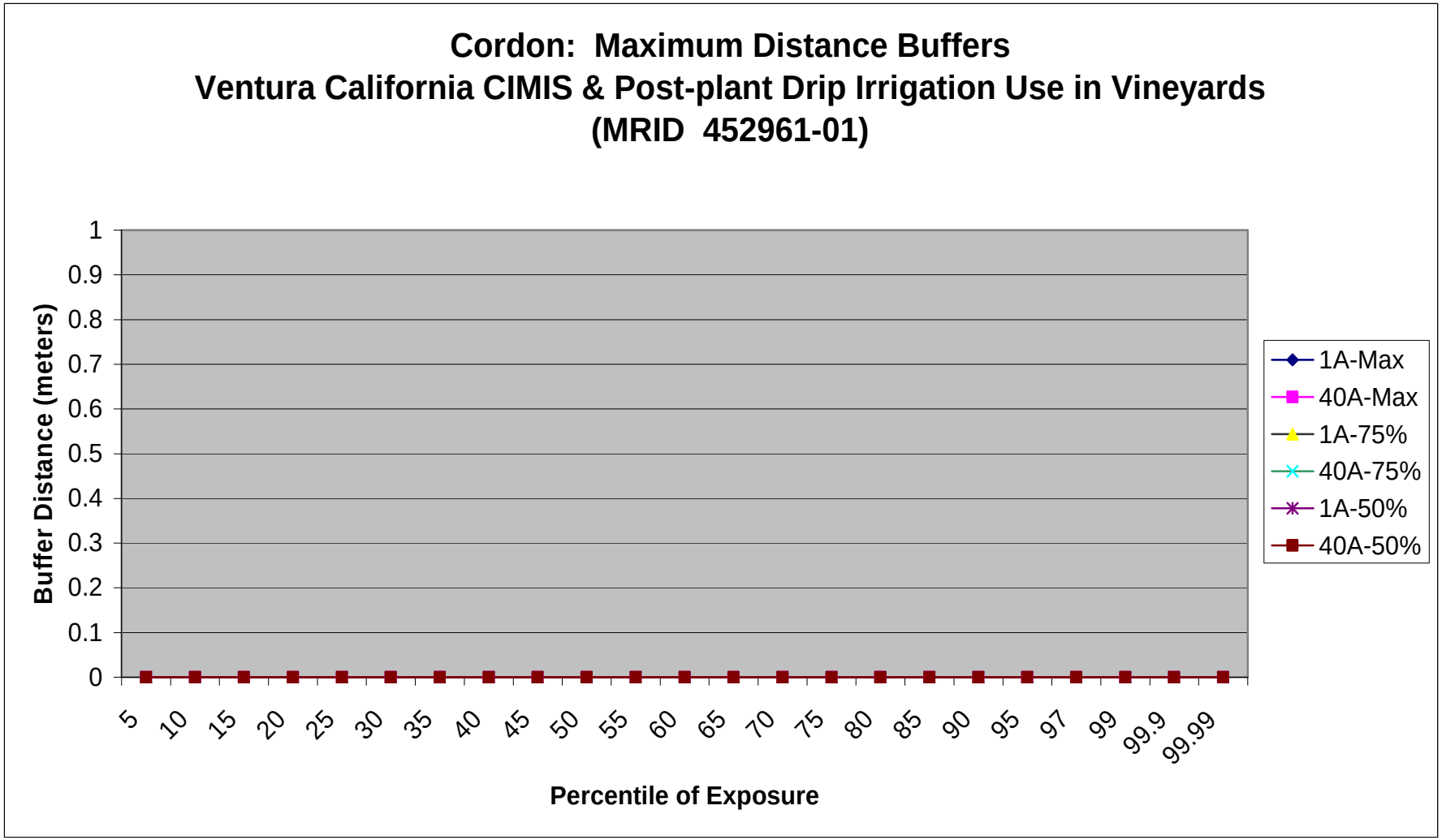
HEC Array for Occupational Risk Assessments¶												
Relevant Study		**LOAEL (ppm)**	**NOAEL (ppm)**	**Da**	**Dh**	**Wa**	**Wh**	**RGDR***	**HEC (ppm)**	**inter**	**Intra**	**UF**
Acute												
Acute Inhalation Rat		**454**	**Not identified**	**4**	**8**	**1**	**1**	**1**	**227.00**	**3**	**10**	**1**
Short Term												
Dominant Lethal Study - Rats		60	10	6	8	5	5	1	7.50	3	10	1
Initiation/Promotion Mechanistic Study Mice	Systemic	60	Not identified	6	8	5	5	1	45.00	3	10	3‡
30 Day Inhalation Mice		Not identified	30	6	8	5	5	1	22.50	3	10	1
30 Day Inhalation Rats		Not identified	30	6	8	5	5	1	22.50	3	10	1
Devel Rat	Maternal Systemic	20	Not identified	6	8	5	5	1	15	3	10	3‡
	Developmental	120.0	60	6	8	5	5	1	45	3	10	1
Dev Rabbit	**Maternal**	**60**	**20**	**6**	**8**	**5**	**5**	**1**	**15**	**3**	**10**	**1**
	Developmental	Not identified	120	6	8	5	5	1	90.00	3	10	1
Initiation/Promotion Mechanistic Study Mice	Systemic	60	Not identified	6	8	5	5	1	45.00	3	10	3‡
Intermediate Term												
13-Week Inhalation Mouse	Local	30	10	6	8	5	5	0.157	1.18	3	10	1
13-Wk Inhalation Rat	**Local**	**30**	**10**	**6**	**8**	**5**	**5**	**0.115**	**0.86**	**3**	**10**	**1**
Initiation/Promotion Mechanistic Study - Mice	systemic	60	Not identified	6	8	5	5	1	45.00	3	10	3‡
Long Term												
Chronic Oncogenicity Rat	Systemic	60	20	6	8	5	5	1	15.00	3	10	1
	Local	60	20	6	8	5	5	0.204	3.06	3	10	1
Chronic Oncogenicity	Systemic	20	5	6	8	5	5	1	3.75	3	10	1
Mouse	**Local**	**20**	**5**	**6**	**8**	**5**	**5**	**0.204**	**0.77**	**3**	**10**	**1**

HEC Array for Occupational Risk Assessments¶												
Relevant Study		**LOAEL (ppm)**	**NOAEL (ppm)**	**Da**	**Dh**	**Wa**	**Wh**	**RGDR***	**HEC (ppm)**	**inter**	**Intra**	**UF**
MultiGen Repro: Rat§	Parental Systemic	90	30	6	8	5	5	1	22.50	3	10	1
	Parental Local	90	30	6	8	5	5	0.204	4.59	3	10	1
Cancer Risk												
Chronic Oncogenicity Mouse	Bronchioalveolar adenomas ♂	60	20	6	8	5	5	3.21	48.15	$Q_1^* = 9.5 \times 10^{-3}$ µg/m³		

¶ Bolded studies used for endpoint selection
‡ 3X UF for LOAEL to NOAEL extrapolation is being recommended due to the mild nature of effects (decreased body weight) noted at the LOAEL
§ Offspring were not directly exposed to the compound
* Input parameters for the derivation of RGDRs were obtained from "Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry" (USEPA, 1994) Tables 4-4, 4-5, and 4-6.

Key for Array Table
LOAEL: Lowest observed adverse effect level
NOAEL: No observed adverse effect level
Da: Daily animal exposure (hrs/day)
Dh: Anticipated daily human exposure (hrs/day)
Wa: Weekly animal exposure (days/week)
Wh: Anticipated weekly human exposure (days/week)
RGDR: Regional Gas Dose Ratio
HEC: Human Equivalent Concentration
inter: interspecies extrapolation uncertainty factor
intra: intraspecies variation uncertainty factor
UF: Other uncertainty factor(s)

Appendix C: Summary Of Cordon® PERFUM Buffer Distributions Based On Ventura California Weather And Data for Post-plant Drip Irrigation Use in Vineyards Data


Cordon: Maximum Distance Buffers
Ventura California CIMIS & Post-plant Drip Irrigation Use in Vineyards
(MRID 452961-01)
Buffer Distance (meters)
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
5
10
15
20
25
30
35
40
45
50
55
60
65
70
75
80
85
90
95
97
99
99.9
99.99
Percentile of Exposure
1A-Max
40A-Max
1A-75%
40A-75%
1A-50%
40A-50%

D312607/Appendix D

Table 1: Summary Of Cordon® PERFUM Buffer Distributions Based On Ventura California Weather And Data for Post-plant Drip Irrigation in Vineyards For Maximum Values

PERFUM (Compiled On 2/1/2006)
Highest Interval Reported (Day X)
HEC (ug/m3) (UF): 343440 (30)
Threshold (ug/m3): 11448
Summary is based on maximum values for each field size

Percentiles	Max (17.74 lbs ai/Acre)		75% (13.31 lbs ai/Acre)		50% (8.87 lbs ai/Acre)	
	1 Acre Square	40 Acres Square	1 Acre Square	40 Acres Square	1 Acre Square	40 Acres Square
5	0	0	0	0	0	0
10	0	0	0	0	0	0
15	0	0	0	0	0	0
20	0	0	0	0	0	0
25	0	0	0	0	0	0
30	0	0	0	0	0	0
35	0	0	0	0	0	0
40	0	0	0	0	0	0
45	0	0	0	0	0	0
50	0	0	0	0	0	0
55	0	0	0	0	0	0
60	0	0	0	0	0	0
65	0	0	0	0	0	0
70	0	0	0	0	0	0
75	0	0	0	0	0	0
80	0	0	0	0	0	0
85	0	0	0	0	0	0
90	0	0	0	0	0	0
95	0	0	0	0	0	0
97	0	0	0	0	0	0
99	0	0	0	0	0	0
99.9	0	0	0	0	0	0
99.99	0	0	0	0	0	0

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Appendix D: Summary Of 1,3-D Bystander Exposure from Known Area Sources Estimated Using the Monitoring Method

Summary of Bystander Exposure from Known Area Sources Estimated Using the Monitoring Method

When assessing bystander exposure to 1,3-D, HED evaluated pre-plant agricultural field fumigations; post-plant drip irrigation fumigations and turf fumigations.

The use of the field volatility data in this assessment is based on the previous bystander exposure review of 1,3-D. Details of study quality and data analysis can be found in the following memo; REVISED Post-application Non-occupational Bystander Risk Estimates for Proposed Label Change from 300 to 100 foot Buffer Zone for Telone II, Telone C-17, and Telone C-35, S.Weiss, D284547, 11/1/02).

In summary, twenty studies, with field volatility data collected near 1,3-D treated fields, have been submitted to the Agency since 1989. Some of the studies (MRID#s 426973-01, 427742-01, 428456-01) reflect application methods that are no longer used, and therefore are not included in this assessment. Eleven of the studies are used to estimate risk for bystander exposure from the broadcast and row uses of 1,3-D. Several studies (MRID#s 447956-02, 451129-02, 452961-01) are used to estimate use drip application methods. Bystander inhalation exposure estimates for the turf uses of 1,3-D are based on air concentration measurements reported in field volatility studies, MRID 451207-01 and 451207-02. One field volatility study is available to address off-site exposure resulting from the post-plant use. Bystander inhalation exposure estimates are based on air concentration measurements reported in this study, (MRID 452961-01). Study descriptions are available in Appendix A of Memo, S.Weiss, D284548, 11/1/02.

Generally, HED calculates non-cancer risks (i.e. acute, short-, intermediate-term, and chronic exposure) using maximum label application rates and cancer risks using “typical” rates. The registrant suggests that the field volatility study were conducted at typical rates(from 96 to 224 lb ai/A). BEAD states these rates would be typical for all crops except for tree/vine crops and pineapples. Since these two crops only accounted for about 9 percent of the total pounds of 1,3-D applied , the rates in the field volatility studies cover the majority of current uses. However, HED risk estimates must reflect the entire range of potential exposures, including those at the high end of the exposure distribution. Therefore, when appropriate, risk calculations are adjusted to account for the maximum label application rate (linear extrapolation) and risks are calculated for both the typical and maximum rates. Cancer risk is calculated based on typical rates only.

Acute MOEs are calculated by comparing the maximum 24 hour time-weighed average (TWA) from each field volatility study to the toxicological human equivalent concentration (HEC) selected for acute risk assessment.

Consistent with the most recent review of bystander exposure (Memo, S.Weiss, D284548, 11/1/02), the consecutive seven day average air concentration were also estimated from each field volatility study. The highest average seven day average each direction is compared to the selected HEC to estimate short-term risk for bystanders.

This is consistent with the pattern of toxicity observed in short-term guideline toxicity studies. In the study used for the short-term risk assessment - the developmental toxicity study in rabbits - the endpoint of concern is a decrease in body weight gain. This effect was not observed until several days after exposure began suggesting that a multiple-day rolling average is appropriate to assess risks.

In the field volatility studies, 1,3-D peak offgassing occurs 1 to 3 days after application. Additionally since 1, 3-D products are used only 1 to 2 times per field each year, the majority of bystander exposure resulting directly from treatment of agricultural fields is expected to be acute or short-term. Intermediate-term exposure (consecutive exposures lasting 30 days to several months) is expected to be less likely. Chronic exposure is not expected since it unlikely that bystanders will be continually exposed to significant concentrations of 1,3-D for 6 consecutive months or longer.

Cancer risks are calculated using the average air concentration for all locations (extrapolated from each field volatility study). It is assumed that the number of days of exposure per year is equal to the number of days that samples were taken in each study (i.e. 7 to 21 days). Since inter-year and seasonal variability in wind direction will prevent any single location from being predominately down wind, using the average air concentration of all directions is appropriate to assess cancer risk resulting from a lifetime of exposure.

None of the acute or short-term risks exceed HED's LOC. Using the average air concentrations, several of the estimated cancer risks exceed HED's LOC for cancer for the existing pre plant uses (generally 1×10^{-6}). Since a particular field is not likely to be treated more than once or twice each year, and a bystander is not likely to be present downwind of the field during this entire period, every year for 50 years, after every application, this assessment is expected to provide an upper-end estimate of cancer risk. Bystander exposure resulting from the agricultural and golf course uses of 1,3-D are summarized in Tables E1 through E3.

Table E1. Acute Non-Cancer Risk for Bystander Exposures Based on Field Volatility Data						Maximum 24 hr TWA Air Concentration			Acute MOE[1]	
#	Study Location/	MRID#	Formulation	Application Rate		Distance (m)	study (ppm)	label max (ppm)	study	label max
				study (g/A)	label max (g/A)					
Broadcast Applications										
2	Imperial Valley, CA; 1989	422657-01	Telone II	12.1	35	30	0.008	0.022	9800	3400
3	Salinas Valley, CA; 1992	425451-01	Telone II	12.3	35	30	0.009	0.027	8100	2800
16	Collier County, FL; 1999	451207-02	Telone II	5.12	35	30	0.018	0.125	4100	610
17	Highlands County, FL; 1998	451207-01	Telone II	5.19	35	30	0.070	0.469	1100	160
18	Waushara County, WI; 2001	454002-03	Telone II	26.8	35	61	0.015	0.020	4900	3800
16	Collier County, FL; 1999	451207-02	Telone II	5.12	35	61	0.010	0.070	7400	1100
17	Highlands County, FL; 1998	451207-01	Telone II	5.19	35	61	0.018	0.124	4100	610
Row Applications										
7	San Joaquin Valley, CA; 1995	442585-01	Telone II	12.6	35	30	0.016	0.097	4800	780
19	Immokalee, FL; 2001	454002-02	Telone II	28.40	35	30	0.041	0.050	1900	1500
19	Naples, FL; 2001	454002-02	Telone II	25.30	35	30	0.138	0.191	550	400
6	Moses Lake, WA; 1992	NR424663-01	Telone II	*	*	91	0.191	--	400	--
Drip Irrigation Application										
8	Rio Grande Valley, TX 1998	447956-02	Telone EC	8.65	18	30	0.054	0.112	1400	670
15	Douglas, GA; 2000	451129-02	In-Line	24.6	20.5	30	0.047	0.039	1600	1900
8	Rio Grande Valley, TX 1998	447956-02	Telone EC	8.65	18	91	0.021	0.044	3600	1700
15	Douglas, GA; 2000	451129-02	In-Line	24.6	20.5	91	0.019	0.016	3900	4700
20	Gilroy, CA, 1998 (post-plant)	452961-01	Telone II	5.4	17.74	91	0.001	--	54000	--

1 Acute MOE = HEC (75.67 ppm)/maximum 24 hour TWA

Table E2. Short-Term 1,3-D Risk for Bystander Exposures Based on Field Volatility Data										
					Application Rate		Highest 7-day Air concentration		Short-term MOE[1]	
#	Study Location/	MRID#	Formulation	Distance (m)	study (g/A)	Label max (g/A)	study (ppm)	label max (ppm)	study	label max
Broadcast Applications										
2	Imperial Valley, CA; 1989	422657-01	Telone II	30	12.1	35	0.006	0.017	870	300
3	Salinas Valley, CA; 1992	425451-01	Telone II	30	12.3	35	0.004	0.011	1300	470
16	Collier County, FL; 1999	451207-02	Telone II	30	5.12	35	0.003	0.018	1900	270
17	Highlands County, FL; 1998	451207-01	Telone II	30	5.19	35	0.013	0.085	400	60
18	Waushara County, WI; 2001	454002-03	Telone II	61	26.8	35	0.008	0.010	640	490
16	Collier County, FL; 1999	451207-02	Telone II	91	5.12	35	0.0003	0.002	14000	2100
17	Highlands County, FL; 1998	451207-01	Telone II	91	5.19	35	0.006	0.039	870	130
Row Applications										
7	San Joaquin Valley, CA; 1995	442585-01	Telone II	30	12.6	35	0.006	0.034	900	150
19	Immokalee, FL; 2001	454002-02	Telone II	30	28.40	35	0.024	0.029	210	170
19	Naples, FL; 2001	454002-02	Telone II	30	25.30	35	0.058	0.080	90	60
6	Moses Lake, WA; 1992	NR424663-01	Telone II	91	*	*	0.078	–	60	
Drip Irrigation Applications										
	Rio Grande Valley, TX 1998	447956-02	Telone EC	30	8.65	18	0.012	0.025	420	200
15	Douglas, GA; 2000	451129-02	In-Line	30	24.6	20.5	0.015	0.012	330	400
8	Rio Grande Valley, TX 1998	447956-02	Telone EC	91	8.65	18	0.005	0.011	980	470
15	Douglas, GA; 2000	451129-02	In-Line	91	24.6	20.5	0.006	0.005	900	1100
20	Gilroy, CA, 1998 (post-plant)	452961-01	Telone II	91	5.4	17.74	0.0003		16000	

1 Short-term MOE = HEC(5.0 for short-term)/highest 7 day air concentration.

Table E3. 1,3-D Cancer Risk for Bystander Exposures Based on Field Volatility Data										
					Application Rate		Concentration	Duration (study days)	LADE	Cancer Risk
#	Study Location/	MRID#	Formulation	Distance (m)	study (g/A)	label max (g/A)	average of directions (ppm)		average of directions	average of directions
Broadcast Applications										
2	Imperial Valley, CA; 1989	422657-01	Telone II	30	12.1	35	0.002	8	3.13E-05	5.63E-07
3	Salinas Valley, CA; 1992	425451-01	Telone II	30	12.3	35	0.002	14	5.47E-05	9.85E-07
17	Highlands County, FL; 1998	451207-01	Telone II	30	5.19	35	0.004	14	1.09E-04	1.97E-06
16	Collier County, FL; 1999	451207-02	Telone II	30	5.12	35	0.0004	13	1.02E-05	1.83E-07
18	Waushara County, WI; 2001	454002-03	Telone C-17	61	26.8	35	0.003	15	8.80E-05	1.58E-06
16	Collier County, FL; 1999	451207-02	Telone II	91	5.12	35	0.0003	13	7.63E-06	1.37E-07
17	Highlands County, FL; 1998	451207-01	Telone II	91	5.19	35	0.002	14	5.48E-05	9.86E-07
Row Applications										
7	San Joaquin Valley, CA; 1995	442585-01	Telone II	30	12.6	35	0.001	21	4.11E-05	7.39E-07
19	Immokalee, FL; 2001	454002-02	Telone II	30	28.4	35	0.009	7	1.23E-04	2.22E-06
19	Naples, FL; 2001	454002-02	Telone II	30	25.3	35	0.023	7	3.15E-04	5.67E-06
6	Moses Lake, WA; 1992	NR424663-01	Telone II	91	*	*	0.027	10	5.28E-04	9.50E-06
Drip Irrigation Applications										
8	Rio Grande Valley, TX 1998	447956-02	Telone EC	30	8.65	18	0.002	8	3.13e-05	5.630E-07
15	Douglas, GA; 2000	451129-02	In-Line	30	24.6	20.5	0.005	9	8.81e-05	1.58E-06
8	Rio Grande Valley, TX 1998	447956-02	Telone EC	91	8.65	18	0.001	10	1.95e-05	3.52E-07
15	Douglas, GA; 2000	451129-02	In-Line	91	24.6	20.5	0.002	11	4.31e-05	7.75E-07
20	Gilroy, CA, 1998 (post-plant)	452961-01	Telone II	91	*	*	0.0001	12	2.34E-06	4.23E-08

1 Cancer Risk = Q1*(1.8 x 10^{-2} ppm) x lifetime average daily exposure (LADE) (based on direction with highest concentration for study duration x number of days exposure during study/365 days per year x 50 years/70 year lifetime).

Appendix E: Model Information and History

Industrial Source Complex 3 (ISC3)

ISC3 (http://www.epa.gov/scram001/dispersion_alt.htm) was developed by the U.S. Environmental Protection Agency (EPA) as a replacement for ISC2. ISC3 is a steady-state Gaussian plume model which can be used to assess pollutant concentrations from a wide variety of sources including point and area sources. ISC3 operates in both long-term and short-term modes. OPP has operated the model in short-term mode in its fumigant assessments and used the designation ISCST3. ISCST3 allows for three different types of outputs: (1) summaries of high values (highest, second highest, etc.) by receptor for each averaging period and source group combination, (2) summaries of overall maximum values (e.g., the maximum 50) for each averaging period and source group combination, and (3) tables of concurrent values summarized by receptor for each averaging period and source group combination for each day of data processed. The third output option was used when OPP ran the ISCST3 model. These outputs can be produced all the way down to an hourly basis.

Up until the end of 2005, ISC3 was the Agency's recommended air dispersion model for steady state sources. It should be noted that ISC3 can still be used as an alternative to the recommended models in Appendix W in regulatory applications with case-by-case justification (see Appendix W to 40 CFR Part 51, Section 3.2).

The ISCST3 model allows for the conservative assessment of concentrations of fumigants coming off of treated fields under specific meteorological and application conditions. However, one of the main weaknesses of ISCST3 is in its treatment of calm periods. A calm period in ISCST3 is when the wind speed is less than 1.0 m/s. When this occurs, ISCST3 assumes that there is no wind blowing and assigns a wind speed of 0.0 m/s and this can result in a misrepresentation of the fumigant plume. For the Agency's fumigant assessments, ISCST3 was run using the "regulatory option" for addressing calm periods.

American Meteorological Society/Environmental Protection Agency Regulatory Model (AERMOD)

AERMOD (http://www.epa.gov/scram001/dispersion_prefrec.htm#aermod) was developed by American Meteorological Society (AMS) and the U.S. Environmental Protection Agency (EPA). ISC was replaced by AERMOD as the preferred air dispersion model for near-field, steady state sources in the Agency's Guidelines on Air Quality Models as of December 9, 2005. AERMOD is a Gaussian plume model which can be used to assess pollutant concentrations from a wide variety of sources including point and area sources. AERMOD incorporates air dispersion based on planetary boundary layer turbulence structure and scaling concepts, including treatment of both surface and elevated sources, and both simple and complex terrain. The AERMOD modeling system consists of two pre-processors and the dispersion model. The meteorological preprocessor AERMET, uses meteorological data and surface characteristics to calculate boundary layer parameters (e.g. mixing height, friction velocity, etc.) needed to run AERMOD. The terrain pre-processor AERMAP both characterizes the terrain and generates receptor grids for AERMOD. AERMOD allows for three different types of outputs: (1) summaries of high values (highest, second highest, etc.) by receptor for each averaging period and source group combination, (2) summaries of overall maximum values (e.g., the maximum 50) for each averaging period and source group combination, and (3) tables of concurrent

values summarized by receptor for each averaging period and source group combination for each day of data processed. These outputs can be produced all the way down to an hourly basis.

As the replacement to ISC3, AERMOD currently contains new or improved algorithms for: 1) dispersion in both the convective and stable boundary layers; 2) plume rise and buoyancy; 3) plume penetration into elevated inversions; 4) computation of vertical profiles of wind, turbulence, and temperature; 5) the urban nighttime boundary layer; 6) the treatment of receptors on all types of terrain from the surface up to and above the plume height; 7) the treatment of building wake effects; 8) an improved approach for characterizing the fundamental boundary layer parameters; and 9) the treatment of plume meander. Many of these improvements have little to no effect on OPP's approach to modeling fumigant applications as area sources.

AERMOD allows for the conservative assessment of concentrations of fumigants coming off of treated fields under specific meteorological and application conditions. However, AERMOD has a similar weakness to ISC3 in its treatment of calm periods. A calm period in AERMOD is when the wind speed is less than 1.0 m/s. When this occurs, AERMOD assumes that there is no wind blowing and assigns a wind speed of 0.0 m/s and this can result in a misrepresentation of the fumigant plume. Also, AERMOD does not allow for the probabilistic treatment of variables such as the meteorological conditions.

CALPUFF

CALPUFF (http://www.epa.gov/scram001/dispersion_prefrec.htm#calpuff) is a non-steady-state meteorological and air quality modeling system developed by the Atmospheric Studies Group at TRC Solutions. It is maintained by the model developers and distributed by TRC (http://www.src.com/html/calpuff/calpuff1.htm). CALPUFF v.5 has been adopted by the Agency in its Guideline on Air Quality Models as the preferred model for assessing long range transport of pollutants and on a case-by-case basis for certain near-field applications involving complex meteorological conditions (i.e., non-steady state). The modeling system consists of three main components and a set of preprocessing and postprocessing programs. The main components of the modeling system are CALMET (a diagnostic 3-dimensional meteorological model), CALPUFF (an air quality dispersion model), and CALPOST (a postprocessing package).

The output files that CALPUFF creates for each run include unformatted data files containing grids of time-averaged concentrations, time-averaged dry deposition fluxes, and time-averaged wet deposition fluxes. These outputs in CALPUFF v.5 can be produced all the way down to an hourly basis. The post-processing program CALPOST is designed to produce ranked tabulations of averages of selected concentration data from these data files. CALPOST writes a text file containing the input data summary and output tables.

Although CALPUFF v.5 is on the Agency's guideline for air models, there is also currently a CALPUFF v.6 that has not yet been reviewed by the Agency. CALPUFF v.6 includes a number of technical enhancements over v.5 but the major one that could have effects on OPP's modeling of fumigant emissions is the option to use subhourly (i.e., 1 minute, 5 minute, etc.) meteorological data.

Probabilistic Exposure and Risk model for FUMigants (PERFUM)

PERFUM (http://www.exponent.com/practices/health/PERFUM.html) was developed to address the issue of bystander exposures following agricultural applications of fumigants. The core of the PERFUM modeling system is the US EPA dispersion model ISCST3 which at the time PERFUM was developed was the Agency's recommended air dispersion model for steady state sources. ISCST3 as described above calculates concentrations but is not designed to determine a buffer zone. PERFUM was designed to specifically take the ISCST3 outputs and use them to produce buffer zone outputs in a distributional format.

PERFUM allows users to develop an understanding of the distributions of potential bystander exposures and thus more fully characterize the range of risks resulting to bystanders around treated fields. ISCST3 is an integral part of the PERFUM model and the basic physics and code of ISCST3 remain unchanged. PERFUM essentially provides ISCST3 with daily meteorological data over 5 years as well as flux estimates within the uncertainty of those data. PERFUM then uses this information to create distributional outputs for pre-defined receptor locations.

Fumigant Emissions Modeling System (FEMS)

FEMS (http://www.sullivan-environmental.com) was developed to address the issue of bystander exposures following agricultural applications of fumigants. FEMS allows the user to define a number of options prior to running the model including: the fumigant to be applied, the frequency of fumigation, the sealing method employed, field size and shape, consecutive day/contiguous field applications, application season, the averaging time for the concentrations, and the dispersion model used (ISCST3, CALPUFF v.5, or CALPUFF v.6). FEMS also allows the user to include Monte Carlo treatments of all the key model inputs like meteorological conditions, emissions data, day the application starts, etc.

Once the core dispersion model is selected, FEMS simulates the application of a fumigant and it's off-gassing over a 4 day simulation using 4 hour time steps. The model estimates fumigant concentrations at various receptors beyond the perimeter of the applied field that are matched to the averaging time of interest for the user. Aside from estimating the fumigant concentrations, FEMS keeps track of the number of times that concentrations exceed the concentration of concern at each receptor.

Once FEMS completes the modeling simulation, the distribution of concentrations is computed for each receptor. FEMS produces two main outputs. The first is a frequency distribution that looks at the number of times that concentrations exceed the concentration of concern at each receptor. The second involves establishing the distributions of concentrations for each receptor and then taking the maximum number of periods per averaging time of interest above the concentration of concern and computing them as a function of distance from the field. Buffer zones are then established based on the most conservative concentrations that were modeled as a function of distance.

Soil Fumigant Exposure Assessment System (SOFEA)

SOFEA (http://www.epa.gov/oscpmont/sap/meetings/2004/index.htm) was developed to evaluate and manage human inhalation exposure potential associated with agricultural applications of fumigants. SOFEA calculates fumigant concentrations in air arising from volatility losses from treated fields for entire agricultural regions using multiple sources (treated fields), GIS information, agronomic specific variables, user specified buffer zones and field intervals. SOFEA uses a modified version of ISCST3 as its dispersion model. SOFEA also uses Monte Carlo techniques to vary the following parameters: weather information, field size, application date, application rate, application method, pesticide degradation rates in air, sealing method, field re-treatment, and buffer setbacks.

Multi-year, multiple field simulations can be conducted with SOFEA using random field placement in all agricultural areas or by selectively placing fields in historical or prospective use areas. Regional land use information can be used to refine the placement of treated fields, dispersion calculations, and exposure assessments. SOFEA has been previously used for regulatory decision making in California.