TO: Susan Edmiston, Environmental Program Manager II, Chief **HSM-09002**
Worker Health and Safety Branch

FROM: Joseph P. Frank, D.Sc., Senior Toxicologist *(original signed by J. Frank)*
Worker Health and Safety Branch
(916) 324-3517

DATE: February 13, 2009

SUBJECT: REVIEW OF PROPOSED UPDATE TO THE CALIFORNIA MANAGEMENT PLAN FOR 1,3-DICHLOROPROPENE (TELONE), REGISTRATION TRACKING ID #229499

Attached is Dr. Linda Hall's review memo on Dow AgroSciences (DAS) proposed 2008 Update to the California Management Plan for 1,3-Dichloropropene (1,3-D).

The DAS proposal includes three changes to the management plan currently in place:
(1) to increase the Statewide Township Allocation (aka township cap) from the default level of 90,250 adjusted pounds per township per year to 1.5 times that level;
(2) to allow short-term township allocation exceptions to up to 4.1 times the default level; and
(3) to allow long-term township allocations, specific for selected counties, to increase to 2 to 3 times the default level.

Dr. Hall identified several issues with the proposal that could lead to an adverse impact on the health of individuals exposed to 1,3-D and recommends against the proposal. Her concerns are as follows:

- The increases are justified by the concept that "borrowing" from low use years to justify high use years will not increase the cancer risk for populations residing in areas of 1,3-D use. The Department of Pesticide Regulation (DPR) scientists do not agree and suggest that this practice could increase cancer risk.

- The proposal is not consistent with a previous understanding between DPR and DAS that modeling methods would be specified by DPR scientists and that they would incorporate the most recent county-specific data available.

- The DAS justification is inconsistent with DPR practices for exposure assessment and is likely to underestimate health risks associated with the proposed changes.

- Modeling studies by DPR scientists indicate that the current agreement which allows 1.5 to 2.0 times the default allocation level, exceeds a cancer risk of $1x10^{-5}$. DPR scientists

believe that further increases in allowable uses would increase the concern for potential adverse health effects.

I have reviewed Dr. Hall's review and recommendation and concur with her findings.

Attachments

cc: Marylou Verder-Carlos, Ph.D., Assistant Director
Gary T. Patterson, Ph.D., Chief, Medical Toxicology Branch
John S. Sanders, Ph.D., Chief, Environmental Monitoring Branch
Ann Prichard, Chief, Registration Branch

TO: Joseph P. Frank, D.Sc., Senior Toxicologist
Worker Health and Safety Branch

FROM: Linda M. Hall, Ph.D., Staff Toxicologist (Specialist) *(original signed by L. Hall)*
Worker Health and Safety Branch
(916) 445-3631

DATE: February 13, 2009

SUBJECT: REVIEW OF PROPOSED UPDATE TO THE CALIFORNIA MANAGEMENT PLAN FOR 1,3-DICHLOROPROPENE (TELONE) DPR VOLUME #50046-0191, REGISTRATION TRACKING ID #229499

Abstract
The 2008 Update to the California Management Plan for 1,3-Dichloropropene (1,3-D) proposes three changes: (1) to increase the Statewide Township Allocation (aka township cap) from the default level of 90,250 adjusted pounds per township per year to 1.5 times that level; (2) to allow short-term township allocation exceptions to up to 4.1 times the default level; and (3) to allow long-term township allocations, specific for selected counties, to increase to 2 to 3 times the default level. There are several concerns about these increases.

The first concern is that the increases are justified by the concept that "borrowing" from low use years to justify high use years will not increase the cancer risk for populations residing in areas of 1,3-D use. Department of Pesticide Regulation (DPR) scientists do not agree and suggest that this practice may actually increase cancer risk.

The second concern is that the proposal ignores a previous understanding between DPR and Dow AgroSciences (DAS) that requests for increases should be justified by the use of modeling methods specified by DPR scientists and should incorporate the most recent county-specific data available.

The third concern is that the measures of the safety used by DAS to justify the proposed increases are not consistent with current DPR practices for exposure assessment and are likely to underestimate health risks associated with the proposed changes.

The fourth concern is that modeling studies by DPR scientists indicate that exposures following applications at 1.5 to 2.0 times the default allocation level already exceed a cancer risk of $1x10^{-5}$. DPR scientists believe that further increases will result in higher risk. For example, application rates of 2 times the default level result in risk values that are 17 to 50% above the 95^{th} percentile for a $1x10^{-5}$ risk. Even application rates of 1.5 times the default level bracket the 95^{th} percentile risk level and result in upper bound risks ranging from 18 to 28% above the $1x10^{-5}$ level. The modeling used township allocation levels of 1.5 to 2.0 times the default whereas the proposed

allocations range up to 4.1 times the default. In view of the resulting excessive risk exposures, approval of the proposal is not recommended at this time. Finally, it is noteworthy that independently conducted monitoring for 1,3-D in the community of Parlier supports modeling estimates generated by DPR scientists.

2008 Proposed California Management Plan Update

Under review is the Proposed Update to the California Management Plan for 1,3-Dichloropropene (1,3-D) dated 1 July 2008 (Bret, 2008) and submitted by DAS to Dr. Tobi Jones (California Department of Pesticide Regulation) on 17 July 2008. In the update, DAS is proposing three changes:

1. **Increase the Statewide Township Allocation** (aka township cap) from the baseline of 90,250 adjusted pounds of 1,3-dichloropropene per township per year (adj lbs 1,3-D/twp/yr) to 135,375 adj lbs 1,3-D/twp/yr. (The 135,375 adj lbs will be referred to as 1.5 times the default level.)

2. **Allow Short-term Township Allocation Exceptions** so that a township that has not exceeded 135,375 lbs as a multi-year average dating back to 1995 may use up to 370,000 adj lbs 1,3-D/twp/yr for a single year. (The 370,000 adj lbs will be referred to as 4.1 times the default level.)

3. **Establish Long-term Township Allocations Specific for Selected Counties** as follows:
    A. **Township Baseline Allocation of 270,750 adj lbs 1,3-D/twp/yr for**:
        i. Kern 31S-29E
        ii. Monterey 14S-03E
        iii. Santa Barbara 10N-34W
        iv. Ventura 2N-22W, 2N-21W, 1N-21W
        v. Imperial 16S-15E

        (The 270,750 adj lbs will be referred to as 3 times the default level.)
    B. **Township Baseline Allocation of 180,500 adj lbs 1,3-D/twp/yr for**:
        i. Merced 6S-11E, 7S-11E, 6S-12E, 7S-12E
        ii. Ventura 1N-22W

        (The 180,500 adj lbs will be referred to as 2 times the default level.)

Concerns about 2008 Proposed Changes to the California Management Plan

I have concerns about the changes proposed by DAS. The first concern is that DPR scientists do not agree with the concept of averaging 1,3-D exposures over periods of more than one year. DPR scientists are not aware of any scientific basis to justify the "borrowing" from low use years for use in risk calculations (Reed, 2003; Johnson, 2008). In fact, biological reasoning would suggest that the practice of elevating use in subsequent years following low use years would increase cancer risk. A detailed explanation of DPR's "biological reasoning" is given in Appendix I (attached): Arguments Against the Proposal to "Borrow" from Low Use Years to Justify Increasing Current Township Caps.

The second concern is that the proposal itself is not consistent with a long-standing understanding between DPR and DAS that requests for increases should be justified by use of the Soil Fumigant Exposure Assessment (SOFEA) modeling system (Johnson, 2008). The SOFEA model was developed specifically to analyze long term air concentrations of 1,3-D resulting from application of 1,3-D containing fumigants. Communications between DPR and DAS over several years reflect this understanding (Johnson, 2008). It was recommended that use of the SOFEA model follow certain guidelines:

(1) The SOFEA version maintained by Bruce Johnson was recommended for use.

(2) The lower/upper bound methodology described by (Johnson and Powell, 2005) was recommended for use.

(3) High End Exposure V5 Crystal Ball (HEE5CB) was recommended for exposure assessment.

(4) A transparent basis for crop/application/section weightings and related information was recommended (Bruce Johnson, personal communication).

A third concern is that DAS uses the 1997 DPR Exposure Assessment and Risk Assessment Document (DPR, 1997) as a measure of the safety of the proposed changes. The California Exposure Assessment and Risk Assessment documents for 1,3-dichloropropene are being updated based on changes [summarized, in part, in (Powell, 2004)] that have occurred since 1997. These changes include (but are not limited to):

1. Introduction of additional 1,3-D containing products and uses in California

2. Additional data on worker exposure

3. Lower acute No-Observed-Effect Level (NOEL) based on new toxicological data (Reed, 2001)

4. Revised default values for body weights and respiration rates for infants, children, and adults (Andrews and Patterson, 2000)

5. New Worker Health and Safety (WHS) Branch practice of using the 95^{th} percentile for daily exposure instead of the geometric mean (Frank, 2009)

6. New WHS practice of using the arithmetic mean instead of the geometric mean, and changes in the method of estimating exposure frequency and duration for longer term exposures (Powell, 2003)

7. Revised modeling approaches by the Environmental Monitoring (EM) Branch to estimate air concentration (off-gassing) for calculating bystander exposures

8. Current data on seasonal use patterns which show that the high use season extends over a longer period than previous estimates

9. Strong justification by DPR (Powell, 2006) for using a 70 year lifetime residency in a high 1,3-D use area, rather than the 30 year residency used by DAS for exposure assessment

In this memorandum, we review estimates for exposure and risk to bystander populations exposed to 1,3-dichloropropene under several scenarios. We evaluate how the proposed 2008 update of the California Management Plan for 1,3-dichloropropene (Bret, 2008) will affect exposure and risk for bystander populations.

1,3-Dichloropropene Use in California

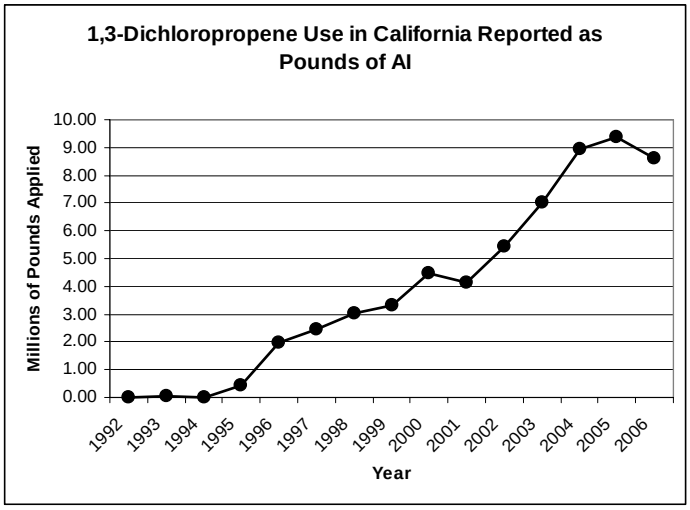


Figure 1. Annual use of 1,3-dichloropropene plotted as total pounds of AI applied per year.

As shown in Figure 1, changes in California regulations have had major effects on the use of 1,3-dichloropropene across the state. Prior to 1990, 1,3-D use averaged ~25 million pounds per year (DPR, 2002). In April 1990, DPR suspended 1,3-D use after the California Air Resources Board monitoring stations in the Central Valley detected levels of concern of 1,3-D in the ambient air. When the suspension of 1,3-D use was lifted in 1995 and a township cap of 90,250 adjusted pounds per year per township was imposed, the annual use over a 5 year period increased to over 4 million pounds per year. In January 2002, township use was allowed at 180,500 adjusted pounds per township per year for those townships where, since 1995, annual use was under the allowed 90,250 pound cap. Over the next 5 years, there was a more than two-fold further increase in the annual use of 1,3-D bringing the use to ~9 million pounds per year. This is ~36% of the level used prior to the 1990 suspension.

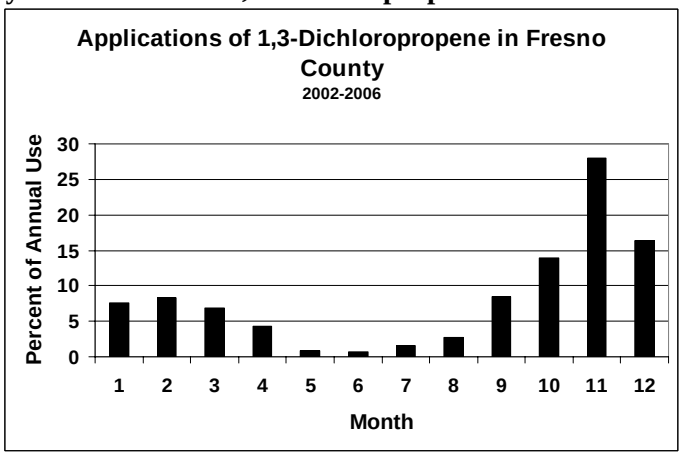
Approximately 10 years of changing regulations, coupled with the phase-out of methyl bromide, has resulted in a large increase of 1,3-D use. Large increases may lead to underestimation of health risks when risk estimates are based on older use patterns rather than current use patterns.

Seasonal Bystander Exposure

Analysis of the Pesticide Use Report (PUR) database for the years 2002 to 2006 reveals distinct seasonal 1,3-D application patterns that vary from county to county. The top use counties (in decreasing order of pounds 1,3-D applied per year) are: Fresno, Kern, Merced, Monterey, Tulare, Stanislaus, Ventura, and Imperial. For these counties, the average annual use varies from 5.59 to

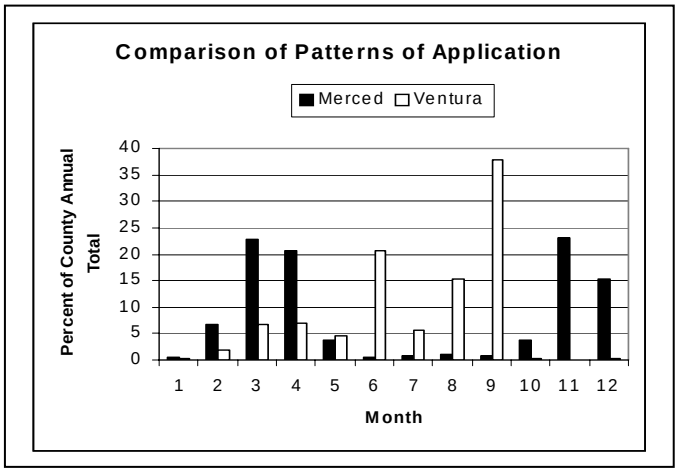
2.72 million pounds of 1,3-D per county per year and the high use season varies from 5 to 8 months. "High use" season is defined as those months in which ≥5% of the total annual amount used in that county is applied in a given month. The seasonal application pattern for the highest use county (Fresno) is shown below in Figure 2. Fresno County shows 7 months of "high use" (January through March and September through December).

Figure 2. Monthly Use Pattern for 1,3-Dichloropropene in Fresno County for 2002-2006



As illustrated in Figure 3, some high use counties, such as Merced (rank #3) and Ventura (rank #7), have non-overlapping high use periods extending collectively over a total of 9 months or more. Therefore, it would be possible to have a longer seasonal exposure by traveling among several counties.

Figure 3: Non-overlapping use patterns between counties



This extended high use season calls into question the early exposure estimates that assumed a 90 day high use season (Sanborn and Powell, 1994; DPR, 1997). Yet this assumption is still being cited in DAS documents. The data summarized in Figures 2 and 3 suggest a much longer seasonal exposure than previously considered.

Township Cap Analysis
Township caps were originally set for California in 1994 to manage cancer risks that are potentially associated with long-term inhalation exposure to 1,3-dichloropropene. Since the time these caps were set, sophisticated modeling methods including: SOFEA, High End Exposure V5 Crystal Ball [HEE5CB] and the Industrial Source Complex Short-Term modeling method Version 3 (ISCST3) have been developed and updated to assess exposure associated with different levels of 1,3-D use and different buffer zones.

Modeling Merced County Townships at 2X the Default Township Cap
In terms of average pounds of 1,3-D applied per year per county over the time period from 2002 to 2006, Merced ranks as the third highest use county in California. Table 1 shows risks derived from patterns of actual use during the period of 2003-2005 and from five year meteorological conditions specific for this high use county (Johnson, 2007a; Johnson, 2007c). These simulations used a level of 180,500 adjusted pounds per township per year for 1,3-D. This level is twice the default township cap. The details of the modeling procedure are given elsewhere (Johnson, 2007a; Johnson, 2007c). Two scenarios were considered: **low mobility** in which residents spend their entire lifetime within a high use township (36 square miles) and **intermediate mobility** in which residents spend their entire lifetime within a 3x3 township area of 324 square miles with the majority of time spent in the highest use township. The more conservative estimate is the low mobility scenario because it uses exclusively the highest exposure township and assumes that a lifetime is spent within that township. For each scenario lower and upper bound exposure estimates were calculated at the 95^{th} percentile level. Lifetime adsorbed daily doses (LADD) in ug/kg-day were converted into risk estimates by multiplying the LADD by $5.5x10^{-5}$ kg-day/ug (Reed, 2001).

DPR directs 1,3-D regulatory efforts towards the 95^{th} percentile risk level (Gosselin, 2001). For 1,3-D the 95^{th} percentile risk is $1.0x10^{-5}$ (Gosselin, 2001). Those risk values in Table 1, which exceed this reference level, are highlighted in bold with a gray background. Based on patterns of actual use of 1,3-D in the townships under consideration, for **both** scenarios, **all** risk estimates are above the reference level. For males, the lifetime cancer risk is 35 to 50% above the regulatory target level for the low mobility scenario and 17-31% above for the intermediate mobility scenario. For women, the risk is 32 to 46% above the regulatory target level for the low mobility scenario and 18-31% above for the intermediate mobility scenario.

Table 1: Risk Estimates Based on Patterns of Actual Use for Merced Township Showing Upper & Lower Bound Estimates for Low & Intermediate Mobility Exposure Scenarios

Bystander Category		Use Data from 2003-2005 (Modeled use @ 2.0 times default cap maximum)	
		Lower Bound Risk	**Upper Bound Risk**
Male	Low Mobility	**$1.35x10^{-5}$**	**$1.5x10^{-5}$**
Male	Intermediate Mobility	**$1.17x10^{-5}$**	**$1.31x10^{-5}$**
Female	Low Mobility	**$1.32x10^{-5}$**	**$1.46x10^{-5}$**
Female	Intermediate Mobility	**$1.18x10^{-5}$**	**$1.31x10^{-5}$**

Long Term Air Concentrations: These risk estimates are based on SOFEA simulations of long term air concentration using a level of 180,500 adjusted pounds of 1,3-D per township per year. This level is twice the default township cap. Other details concerning the models and assumptions used in calculating these risk estimates are given elsewhere (Johnson, 2007a; Johnson, 2007c).
Risk Estimates: SOFEA simulation of the cumulative frequency distribution of long term air concentrations were entered into an exposure simulation model (HEE5CB) along with body weights, breathing rates and other parameters to produce a frequency distribution of lifetime exposures. Exposures were converted to risk by multiplying the upper bound or lower bound LADD by the upper bound potency factor of $5.5x10^{-5}$ kg-day/ug (Reed, 2001)
Low Mobility assumes that residents spend their entire lifetime within the highest use township (36 square miles). This is the most conservative scenario.
Intermediate Mobility assumes that residents spend their lifetime within a 9 township area of 324 square miles, but reside in and spend the greater part of time in the highest use township.
Lower Bound Risk and Upper Bound Risk bracket the 95^{th} percentile.
Reference Level for 1,3-D risk is $1.0x10^{-5}$ (Gosselin, 2001). Bolded numbers within shaded boxes exceed this regulatory target level.

The conclusion is that township allocations of twice the default township cap of 90,250 pounds per year are "unsustainable" in relation to the reference level (Johnson, 2007c). Given these risk estimates for the selected high use townships in Merced, even higher cap levels such as those proposed in the 2008 Update of the California Management Plan (Bret, 2008) are not recommended. At the very least, additional modeling is required for the new, high use scenarios proposed by DAS to judge the impact this will have on exposure (Johnson, 2008).

Modeling Ventura County Townships at 1.5X the Default Township Cap
The conclusion that increasing township caps cannot be recommended (without additional township specific modeling and risk analysis) is further justified by risk estimates for Ventura, another 1,3-D high use county. When averaged over the five year period from 2002-2006, Ventura county ranks seventh in California in terms of pounds of 1,3-D applied per year. The simulations for Ventura risk estimates are described in detail by Johnson (Johnson, 2007b). These calculations used a configuration of township caps in a 5x5 township area of high 1,3-D use as proposed by DAS. Four of the inner nine townships were assigned a use level of 135,375

adjusted pounds per township per year (1.5 times the default township cap level). The remaining 21 townships were modeled at less than 90,250 adjusted pounds per year with 19 of those 21 townships using less than 9025 adjusted pounds per township per year. Note that all of the townships modeled had township levels significantly lower than those being proposed in the 2008 Update of the California Management Plan, which lists long term township allocation for 180,500 adjusted pounds (2x the default township cap) or up to 270,750 adjusted pounds of 1,3-D (3x the default township cap) for specific Ventura townships.

The risk estimations given in Table 2 below are based on three years of Ventura-specific use patterns (from 2003 to 2005) and five years of meteorological data from Ventura. The Low Mobility and Intermediate Mobility scenarios were defined as described above for Merced County. As highlighted in bold in the gray boxes in Table 2 **all** of the Low Mobility scenarios resulted in risks higher than the reference level. For males the bounds for lower and upper 95th percentile for risk were 6 to 28% higher than the reference level while for females they were 4 to 26% higher. For the Intermediate Mobility scenarios, the lower and upper bounds straddled the 95th percentile reference level for both males and females. The upper bounds were 18-19% higher than the reference level.

Table 2. Risk Estimates for Ventura Township Showing Upper & Lower Bound Estimates for Low & Intermediate Mobility Exposure Scenarios

Bystander Category		Modeled use @1.5x default cap maximum	
		Lower Bound Risk	**Upper Bound Risk**
Male	Low Mobility	**$1.06x10^{-5}$**	**$1.28x10^{-5}$**
Male	Intermediate Mobility	$0.95x10^{-5}$	**$1.18x10^{-5}$**
Female	Low Mobility	**$1.04x10^{-5}$**	**$1.26x10^{-5}$**
Female	Intermediate Mobility	$0.96x10^{-5}$	**$1.19x10^{-5}$**

Details concerning the models and assumptions used in calculating these risk estimates are given elsewhere (Johnson, 2007b).
Risk Estimates: SOFEA simulation of the cumulative frequency distribution of long term air concentrations were entered into an exposure simulation model (HEE5CB) along with body weights, breathing rates and other parameters to produce a frequency distribution of lifetime exposures. Exposures were converted to risk by multiplying the upper bound or lower bound LADD by the upper bound potency factor of $5.5x10^{-5}$ kg-day/ug (Reed, 2001)
Low Mobility assumes that residents spend their entire lifetime within the highest use township (36 square miles). This is the most conservative scenario.
Intermediate Mobility assumes that residents spend their lifetime within a 9 township area of 324 square miles, but reside in and spend the greater part of time in the highest use township.
Lower Bound Risk and Upper Bound Risk bracket the 95th percentile.
Reference Level for 1,3-D risk is $1.0x10^{-5}$ (Gosselin, 2001). Bolded numbers within shaded boxes exceed this regulatory target level.

Conclusions and Recommendations

When patterns of county-specific use data from 2003-2005 and county-specific meteorological data for five years are used by DPR in conjunction with the SOFEA modeling tool, air concentration estimates were developed for Merced and Ventura townships. The township levels (1.5x or 2x the default township cap) used in this modeling were equal to or significantly lower than the elevated township levels (ranging up to 4.1x the default township cap) proposed in the 2008 Update of the California Management Plan. The low mobility scenarios for each county gave 95th percentile risk values that were all higher than the reference value for lifetime cancer risk for 1,3-D by 32 to 50% for Merced County and 4 to 28% for Ventura County. The risk values for intermediate mobility scenarios for Merced also were higher than the reference value by 17 to 31% while the risk values for intermediate mobility for Ventura County straddled the reference value with the upper bound estimate being 18-19% higher than the reference value. Increasing the township caps as suggested by the Updated Plan would increase the risk even further beyond the reference level and is not recommended.

The risk estimates presented in this document are based on county-specific use and county-specific meteorological data in Merced or Ventura. These counties rank number 3 and 7, respectively, in terms of pounds of 1,3-D applied per year. In these models, the cancer risk estimates ranged from 0.95×10^{-5} to 1.5×10^{-5} (Tables 1 and 2). Recently, in an independent approach Dr. Jay Schreider (DPR, Medical Toxicology Branch) calculated cancer risk due to 1,3-D exposure in Parlier (Fresno County) to be 3.4×10^{-5} (J. Schreider, personal communication). Fresno County ranks as number 1 in California in terms of pounds of 1,3-D applied per year. Dr. Schreider used the one year average for all the air sampling days and sites in the Parlier area to determine the chronic air levels of 1,3-D used in his cancer risk calculations. Despite the differences in approaches, it is important to emphasize the similarity in bystander cancer risk estimates based air monitoring versus modeling calculations. The calculations by Dr. Schreider will be part of an Environmental Justice Air Quality Report on the community of Parlier (http://www.cdpr.ca.gov/docs/envjust/pilot_proj/parlier_faq_en.pdf).

As discussed above, both existing modeling by DPR scientists and air monitoring studies from Parlier strongly suggest that increases in 1,3-D use to the levels requested by DAS would most certainly result in excessive risk exposures. Thus, I recommend that, in line with long standing agreements, all requests for increases should be justified based on air monitoring and/or modeling done by DPR scientists. I also recommend that the modeling conform to DPR guidelines and policies (Andrews and Patterson, 2000; Andrews, 2001; Powell, 2006; Johnson, 2008). I recommend that new exposure estimates and risk analysis be done by DPR scientists. I recommend that approval of the requested township cap increases be delayed until the data justifying such increases is obtained, reviewed, and approved by DPR scientists.

References

Andrews, C. 2001. Worker Health and Safety Branch Policy on the Estimation of Short-term, Intermediate-term, Annual and Lifetime Exposures. HSM-01014. Sacramento, CA: Worker Health and Safety Branch, Department of Pesticide Regulation, California Environmental Protection Agency. October 4, 2001. http://www.cdpr.ca.gov/docs/whs/memo/hsm00011.pdf

Andrews, C., and Patterson, G. 2000. Interim Guidance for Selecting Default Inhalation Rates for Children and Adults. HSM-00010. Sacramento, CA: Worker Health and Safety Branch and Medical Toxicology Branch, Department of Pesticide Regulation, California Environmental Protection Agency. December 01, 2000. http://www.cdpr.ca.gov/docs/whs/memo/hsm00010.pdf.

Bret, B. L. 2008. Proposed Update to the California Management Plan for 1,3-Dichloropropene. Indianapolis, IN: Dow AgroSciences. (DPR Vol. No. 50046-0191, Record No. 241230. Tracking ID#229499).

DPR. 1997. Risk Assessment of 1,3-Dichloropropene. (January 10, 1997). http://www.cdpr.ca.gov/docs/risk/rcd/dichloro.pdf.

DPR. 2002. California Management Plan: 1,3-Dichloropropene. (January 30, 2002). http://www.cdpr.ca.gov/docs/emon/methbrom/telone/mgmtplan.pdf.

Frank, J. P. 2009. Method for Calculating Short-Term Exposure Estimates. HSM-09004. Sacramento, CA: Worker Health and Safety Branch, Department of Pesticide Regulation, California Environmental Protection Agency. February 9. http://www.cdpr.ca.gov/docs/whs/memo/hsm09004.pdf.

Gosselin, P. 2001. Managing 1,3-d (Telone) chronic risks. Memorandum to Tobi L. Jones, PhD, Ron Oshima, and Douglas Y. Okumura, Department of Pesticide Regulation, dated April 9. Sacramento, CA.

Johnson, B. 2007a. Simulation of Concentrations and Exposure Associated with Dow Agrosciences-Proposed Township Caps for Merced County for 1,3-Dichloropropene. Memorandum to Tobi L. Jones, Ph.D., Division of Registration and Health Evaluation, Department of Pesticide Regulation, from Bruce Johnson, Ph.D., Research Scientist III, Environmental Monitoring Branch, Department of Pesticide Regulation, dated March 29.

Sacramento, CA: Environmental Monitoring Branch, Department of Pesticide Regulation. http://www.cdpr.ca.gov/docs/emon/pubs/ehapreps/analysis_memos/mercd_telone.pdf.

Johnson, B. 2007b. Simulation of Concentrations and Exposure Associated with Dow AgroSciences-Proposed Township Caps for Ventura County for 1,3-Dichloropropene. Memorandum to Tobi L. Jones, Ph.D., Division of Registration and Health Evaluation, Department of Pesticide Regulation, from Bruce Johnson, Ph.D., Research Scientist III, Environmental Monitoring Branch, Department of Pesticide Regulation, dated March 27. Sacramento, CA: Environmental Monitoring Branch, Department of Pesticide Regulation. http://www.cdpr.ca.gov/docs/emon/pubs/ehapreps/analysis_memos/ventur_telone.pdf.

Johnson, B. 2007c. Simulation of Concentrations and Exposure Associated with Updated Township Caps for Merced County for 1,3-Dichloropropene. Memorandum to Tobi L. Jones, Ph.D., Division of Registration and Health Evaluation, Department of Pesticide Regulation, from Bruce Johnson, Ph.D., Research Scientist III, Environmental Monitoring Branch, Department of Pesticide Regulation, dated April 9. Sacramento, CA: Environmental Monitoring Branch, Department of Pesticide Regulation. http://www.cdpr.ca.gov/docs/emon/pubs/ehapreps/analysis_memos/1905_Jones.pdf.

Johnson, B. 2008. Preliminary evaluation of DAS Proposed Update to the California Management Plan: 1,3-Dichloropropene (July 15, 2008). Mini-memorandum to John Sanders, environmental Monitoring Branch, Department of Pesticide Regulation, from Bruce Johnson, Research Scientist III, Environmental Monitoring Branch, Department of Pesticide Regulation, dated August 8. Sacramento, CA.

Johnson, B., and Powell, S. 2005. Interim Statewide Caps Analysis for 1,3-Dichloropropene. HSM-05014. Sacramento, CA: Environmental Monitoring Branch and Worker Health and Safety Branch, Department of Pesticide Regulation, California Environmental Protection Agency. December 28, 2005. http://www.cdpr.ca.gov/docs/whs/memo/hsm05014.pdf.

Powell, S. 2003. Why Worker Health and Safety Branch Uses Arithmetic Means in Exposure Assessment. HSM-03022. Sacramento, CA: Worker Health and Safety Branch, Department of Pesticide Regulation, California Environmental Protection Agency. September 22, 2003. http://www.cdpr.ca.gov/docs/whs/memo/hsm03022.pdf.

Powell, S. 2004. Evaluation of the Need to Revise the Occupational Exposure Assessment for 1,3-Dichloropropene. HSM-04014. Sacramento, CA: Worker Health and Safety Branch, Department of Pesticide Regulation, California Environmental Protection Agency. May 18, 2004. http://www.cdpr.ca.gov/docs/whs/memo/hsm04014.pdf.

Powell, S. 2006. Estimating Residential Mobility for the Assessment of Lifetime Exposure to 1,3-Dichloropropene. HSM-06015. Sacramento, CA: Worker Health and Safety Branch,

Department of Pesticide Regulation, California Environmental Protection Agency. December 31, 2006. http://www.cdpr.ca.gov/docs/whs/memo/hsm06015.pdf.

Reed, N.-M. 2001. Exposure criteria for 1,3-dichloropropene. Memorandum to Gary Patterson, Medical Toxicology Branch, from Nu-may Reed, Staff Toxicologist, Medical Toxicology Branch, Department of Pesticide Regulation, California Environmental Protection Agency, dated February 8. Sacramento, CA.

Reed, N.-M. 2003. Assignment #03-0005. Memorandum to Garry Patterson and Keith Pfeifer, Medical Toxicology Branch, Department of Pesticide Regulation, from Nu-may Reed, Staff Toxicologist, Medical Toxicology, Department of Pesticide Regulation, dated January 24. Sacramento, CA.

Sanborn, J., and Powell, S. 1994. Human Exposure Assessment for 1,3-Dichloropropene. HS-1634. Sacramento, CA: Worker Health and Safety Branch, Department of Pesticide Regulation, California Environmental Protection Agency. July 20, 1994. http://www.cdpr.ca.gov/docs/whs/pdf/hs1634.pdf.

Appendix I: Arguments Against the Proposal to "Borrow" from Low Use Years to Justify Increasing Current Township Caps

In the proposed 2008 Update to the California Management Plan for 1,3-Dichloropropene (1,3-D), Dow AgroSciences (DAS) proposes to increase the current township cap from the default level of 90,250 adjusted pounds per township per year to 1.5 to 4.1 times the default level. These increases are justified by the suggestion that "borrowing" from low use years to justify higher use will not increase the cancer risk for populations residing in the areas of proposed increased 1,3-D caps. California Department of Pesticide Regulation (CDPR) scientists do not agree and suggest that this practice will actually increase cancer risk. Under U.S. Environmental Protection Agency's (U.S. EPA's) 1987 cancer risk assessment guidelines (U.S. Environmental Protection Agency, 1987), 1,3-D is classified as "B2", a probable human carcinogen.

Normal cells develop increasingly neoplastic phenotypes through a multi-step process which is described (Clayson, 2001) as:

(1) **Initiation**: the conversion of normal cells into potentially precancerous cells generally through the accumulation of mutations
(2) **Promotion**: the expansion of clones of initiated cells in response to cytotoxic agents, inflammatory agents, and tumor promoters
(3) **Progression:** the development of tumors to increasing levels of malignancy as a result of a cascade of further critical mutations in neoplastic cells followed by further cell proliferation

Carcinogenic compounds may act by genotoxicity (mutagenic agents) and/or nongenotoxicity (such as cytotoxic agents) (Weinberg, 2007). As shown in Figure 1, these classes have different dose response curves. Up to a certain concentration, mutagens cause a mutational burden in cells that is linearly proportional to the cumulative dose (as shown by the straight red line in Figure 1.). The weight of evidence suggests that 1,3-D acts as a mutagen in the presence of metabolizing enzymes that convert 1,3-D into electrophilic epoxides that interact directly with DNA to cause mutations (Schneider *et al.*, 1998).

A mutagenic action may leave DNA with an accumulation of genetic alterations. Subsequent action by a tumor "promoter" allows mutant cells to proliferate vigorously. Promoters may cause inflammation and/or be mitogenic (stimulate cell division) or cytotoxic (kill cells). Cytotoxicity by tumor promoters causes proliferation of the surviving cells. Tumor promoters have in common the ability to promote expansion of the "initiated" cell clones carrying an accumulation of mutations. This expansion is important because the proliferation provides an opportunity for the accumulation of additional mutations required for the progression from normal cells to tumors. There is evidence that 1,3-D also acts as a cytotoxic agent or tumor promoter. For example, 1,3-D causes chronic irritation, dermatitis, and histopathology involving hyperplasia (accumulation of excessive numbers of normal-appearing cells within a tissue) in organs at the portal of entry and/or in organs involved in excretion of metabolites. Inflammatory cells release reactive oxygen species which may attack and mutate DNA adding to the

mutagenic effects. As shown in Figure 1 (the blue sigmoid curve), promoters/cytotoxic agents act in a nonlinear fashion in tumorigenesis. Once a threshold is exceeded, they show a dramatic increase in tumor formation. Thus, increasing exposure to a carcinogenic agent may not result in a strictly linear response arguing against the "borrowing' concept.

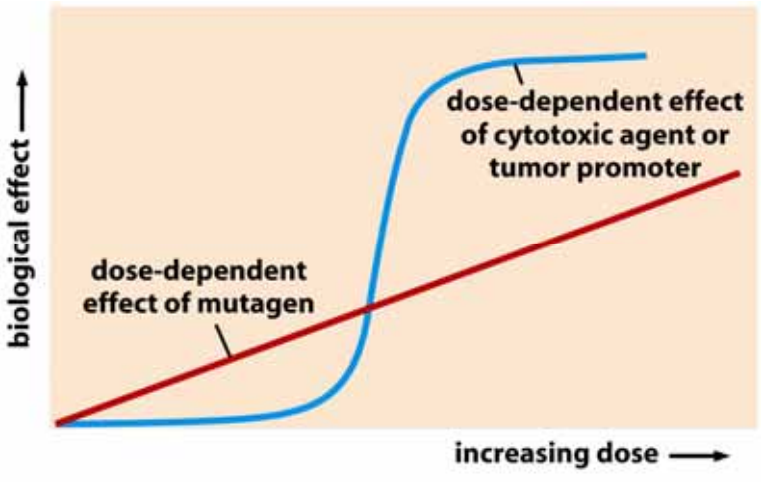


Figure 1: Dose response curves for tumor initiators (mutagens) and promoters.
(Figure 11.42 from Weinberg, 2007)

Indeed, even initiating mutagenic effects will be linear only to a certain point. In Figure 2, the dotted line shows the projected linear accumulation of mutations as a function of dose of mutagen (as shown also in Figure 1). However, as the dose of a mutagen becomes higher, a break in the curve will occur when the rate of mutation formation exceeds the capacity of DNA protection or DNA repair systems. This is illustrated by the solid line in Figure 2. The curve continues to be linear after the break but with a much steeper slope because the mitigating processes have been overwhelmed.

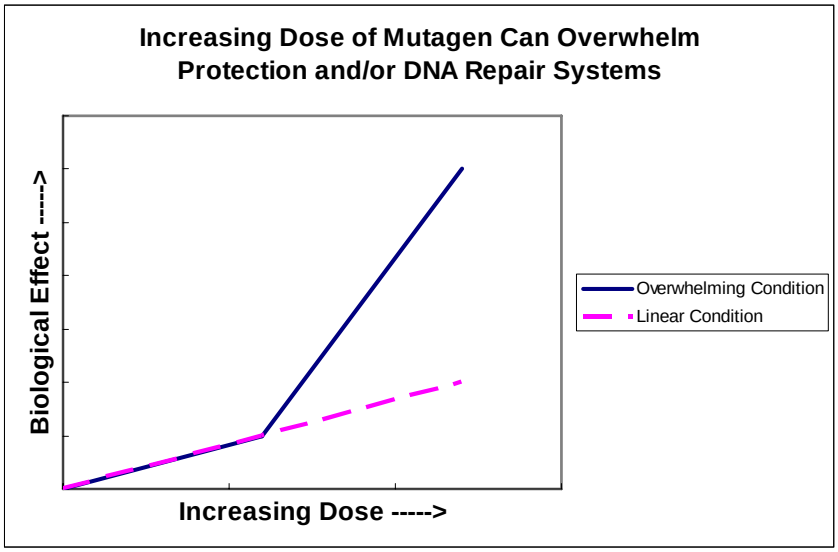


Figure 2: The dose response curve for mutagens will show a break if protection and/or DNA repair systems experience high concentrations of mutagen.

For 1,3-D, higher exposures might cause a steep increase in the curve by at least one of two mechanisms. The DNA repair system will correct at least some of the mutations induced by the epoxide metabolites. However, if the repair system is overwhelmed (or even mutated itself so that it is no longer functional), an increase in the slope will occur. In addition, it is known that glutathione acts as an antioxidant to protect against the mutagenic effects of 1,3-D (Creedy *et al.*, 1984; Watson *et al.*, 1987; Schneider *et al.*, 1998). The levels of glutathione vary among tissues and exposure to high levels of 1,3-D will reduce or deplete glutathione in some cells making them particularly vulnerable to mutagenic effects. This again would lead to a break in the linear curve and result in a much higher mutation rate than predicted by the initial slope. Although not illustrated in Figure 2, there could be multiple breaks in the linear curve due to overwhelming different protective processes and leading to higher mutation rates and thus higher cancer risk than predicted by lower doses.

The acquisition of mutations is thought to be a rate-limiting step in tumor progression. Generally, there is often a 20 year average progression from initiation to tumor progression to clinical cancer in humans (Wogan *et al.*, 2004). Immediate DNA damage is proportional to the dose of mutagen. At higher exposures (such as those which would result from the proposed increased township caps), mutations would build up at a faster rate. This, coupled with promoting events could accelerate the progression to clinical cancer in humans. Taken together, the concepts illustrated in Figures 1 and 2 illustrate why the requested higher township caps could result in much higher cancer risks than exposure at the lower default cap level.

A final argument against justifying increased caps is that, to the best of our knowledge, it has never been the practice of CDPR or the U.S. EPA to average together years of non-use with years of use of a pesticide for the purpose of exposure assessment and risk analysis. We are unaware of a defensible scientific rationale justifying such a practice. Also, it cannot be assumed that there was no earlier exposure prior to the averaging period. In fact for 1,3-D, the products used prior to 1991 had unacceptably high emission potentials and this was the reason for the temporary ban on their use. As pointed out by Dr. Bruce Johnson, DAS attributed a 100% emission potential to 1,3-D products prior to 1991 and an emission potential of 0.4 for use from 1996 to 2003. This suggests that there was a very high chronic exposure prior to 1991 which is not taken into account in the 2008 Proposed Update to the California Management Plan for 1,3-Dichloropropene.

I am very concerned about the attempt to set caps by averaging low use years with proposed higher use years.

References

Clayson, D. B. 2001. Carcinogenesis Mechanisms. In *Toxicological Carcinogenesis* Boca Raton, FL: Lewis Publishers, pp. 113-136.

Creedy, C. L., Brooks, T. M., Dean, B. J., Hutson, D. H., and Wright, A. S. 1984. The protective action of glutathione on the microbial mutagenicity of the Z- and E-isomers of 1,3-dichloropropene. *Chemico-biological interactions* 50:39-48.

Schneider, M., Quistad, G. B., and Casida, J. E. 1998. 1,3-Dichloropropene epoxides: intermediates in bioactivation of the promutagen 1,3-dichloropropene. *Chemical research in toxicology* 11:1137-1144.

U.S. Environmental Protection Agency. 1987. Risk Assessment Guidelines of 1986. . *Office of Health and Environmental Assessment*. (August 1987). EPA/600/8-87/045.

Watson, W. P., Brooks, T. M., Huckle, K. R., Hutson, D. H., Lang, K. L., Smith, R. J., and Wright, A. S. 1987. Microbial mutagenicity studies with (Z)-1,3-dichloropropene. *Chemico-biological interactions* 61:17-30.

Weinberg, R. A. 2007. *Biology of Cancer*. New York: Garland Science.

Wogan, G. N., Hecht, S. S., Felton, J. S., Conney, A. H., and Loeb, L. A. 2004. Environmental and chemical carcinogenesis. *Seminars in cancer biology* 14:473-486.