State of California

Memorandum

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To: James Herota, Registration Specialist
Pesticide Registration Branch

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Place: Sacramento
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From: **Department of Pesticide Regulation** - David Haskell, Associate [original signed by D. Haskell, J. Ross]
Environmental Research Scientist
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Subject: Estimate of Occupational and Non-Occupational Exposure to Sodium Tetrathiocarbonate and Carbon Disulfide from Proposed Registration of Enzone® on grapes and citrus.

The Unocal Corporation has submitted an occupational exposure study in support of the renewal of their federal section 5 registration for Enzone®, USEPA No. 612-EUP-1 and in response to data requirements related to worker health and safety. On July 1, 1989 carbon disulfide was listed under Proposition 65 as an agent known to the State to cause male and female reproductive toxicity and developmental toxicity. The USEPA (1986; 1992) has published a reference dose for carbon disulfide based on a No-Observed-Adverse-Effect-Level (NOAEL) of 11 mg/kg for developmental toxicity. This corresponds to a daily intake by the inhalation route of 1280 mg with 50% absorption for a woman with a body weight of 5 8 kg. The Office of Environmental Health Hazard Assessment, Reproductive and Cancer Hazard Assessment Section (RCHAS), has recommended in the memorandum dated November 6, 1992 to Steven A. Book that the low dose of 22 mg/kg in the rabbit teratology study by Hardin *(et al.*, 1981) be adopted for Proposition 65 purposes. This 22 mg/kg dose with a margin of safety (MOS) of 1000 is equivalent to 22 µg/kg/day. The purpose of this review is to determine if the exposure to the parent compound and its major degradate, carbon disulfide, under the experimental use permit is significant per SB 950. This determination was based in part on whether the observed or calculated exposures to carbon disulfide would be exempt from the warning required by Proposition 65 for substances known to the State to cause reproductive toxicity.

I. Occupational Exposure to Sodium tetrathiocarbonate

Enzone® is formulated as a concentrated solution of the sodium tetrathiocarbonate salt in water at 3.4 pounds per gallon. Sodium tetrathiocarbonate is very water soluble and releases carbon disulfide when the pH is lowered by contact with water and soil. Due to the unstable nature of sodium tetrathiocarbonate, a stable marker of cesium ion in the form of cesiurn chloride was added to the product for exposure monitoring. Since this addition was at a known level (1 µg of cesium ion = 334 µg of sodium tetrathiocarbonate), detection of the cesium ion was used to calculate the amount of sodium tetrathiocarbonate that was present on the dermal dosimeters (long cotton underwear) and in the hand and glove washes before degradation occurred. The cesium ion was detected in the

experimental media through Flame Atomic Emission Spectrometry with validation of the linearity of the calibration curve, the precision of the replicates and the long term stability of the standard and sample solutions. The composition of the test material was 0.0975% cesium and 99.9% product of which 32.6% was sodium tetrathiocarbonate. One µg of cesium detected in the dosimeters was equivalent to 1.02 mg of product or 0.334 mg of exposure to sodium tetrathiocarbonate. The level of cesium was stable (1-3% variation) in the test material through the 14 day test period. Cesium was not detected in the irrigation water or water used in the pretreatment trials. Levels in the soil were very low and not extractable. The efficiency of the extraction method for the hand washes and glove washes was 100% for sample recoveries of the lab spiked samples. Recoveries from spiking the hand and glove wash water averaged 100% for the low spike and 99% for the high spike. The recovery of cesium from the field spiked underwear averaged 102% for the low spike and 100% for the high spike. The limit of detection (LOD) for cesium in dilute aqueous solutions was established as 0.8 µg/L with a limit of quantitation (LOQ) of 2 µg/L. The LOD for cesium on the long cotton underwear dosimeters was 0.04 µg for the swatches and 2.4 µg for the remaining underwear (top or bottom).

The results from analysis of the long cotton underwear dosimeter samples found the majority of the cesium residues were below the LOD or LOQ for all workers. Only one sample from one of the nine workers applying the pretreatment irrigation water had a quantifiable residue of 0.1 µg of cesium. Three of the nine workers applying the active ingredient (a.i.) had residues from the samples above the LOQ. The results from the hand and glove wash samples were similar with the majority of the residues at LOD or LOQ levels. However, for the workers making the mini-sprinkler applications, residues were detected above the LOQ for workers making the pretreatment water or sodium tetrathiocarbonate applications. A Student's t-Test comparing the results of all mini-sprinkler samples, with sample results given a value equal to 1/2 the LOD or the (LOD + LOQ)/2 if the results were not quantifiable, indicated the mean value for the sodium tetrathiocarbonate applications did not differ significantly from the mean value for the pretreatment water applications. The researchers concluded that some background source of cesium at the mini-sprinkler site was impacting the results.

The mean exposure rates for the hand and glove washing samples from the pretreatment water applications and the sodium tetrathiocarbonate applications were compared using the Student's t-Test. Samples with non-detectable residues were given values equivalent to 1/2 the LOD value and those considered detectable but not quantifiable were denoted as (LOD + LOQ)/2. The researchers concluded there was not a significant difference between the levels of cesium detected in the hand and glove wash samples from the water only or sodium tetrathiocarbonate applications. Since the application of sodium

tetrathiocarbonate did not result in any measurable increase in the cesium level, no exposure to sodium tetrathiocarbonate was measured in the hand and glove wash samples. Therefore, the calculations for the hand and washed glove exposures for the workers were made using the LOD value for the cesium ion in water at 0.8 µg/L or 0.08 µg/L for the 100 mL samples. When cesium was not detected in the underwear sample, the value observed was considered 1/2 LOD and values that were above the LOD but were too low to be quantified were expressed as 1/2(LOD + LOQ). All hand and glove wash sample results were estimated using the LOD. Using these conventions, the average dermal exposure for the nine workers, mixing/loading or applying the sodium tetrathiocarbonate was 2.27 mg/day.

The amount of sodium tetrathiocarbonate ultimately absorbed from exposure to the formulated product or to the diluted product in irrigation water will be determined by its physicochemical properties. The amount of sodium tetrathiocarbonate and CS_2 that will eventually be absorbed by the skin will be dependent on the stability of sodium tetrathiocarbonate and the volatility of CS_2. As a salt, sodium tetrathiocarbonate is very soluble in water and remains stable in an aqueous solution with a pH >10. As such, it is not lipophilic and will remain in the water partition and not be absorbed appreciably by the skin. Ionic pesticides e.g. paraquat, diquat, glyphosate and metam-sodium are absorbed < 5% dermally. As the skin buffers the pH downward, sodium tetrathiocarbonate will become unstable and breakdown into CS_2. With a high vapor pressure (300 mm Hg), CS_2 will volatilize rapidly from the skin. An estimated 10% of the initial exposure will remain on the skin as undegraded sodium tetrathiocarbonate. Utilizing the 5% absorption rate for similar ionic pesticides, the estimated daily dose of sodium tetrathiocarbonate absorbed by a 76 kg male worker would be 0.15 µg/kg (2.27 mg x 0.10 x 0.05 x 1000/76 kg). **Based on these very low estimates of the absorbed dosage of the parent compound, the exposure appears to be insignificant.**

II. **Occupational Exposure to Carbon disulfide**

Carbon Disulfide, the primary degradate of the active ingredient of Enzone® (sodium tetrathiocarbonate) in the soil, has been listed as a Proposition 65 Chemical, known to the State to cause male and female reproductive toxicity and developmental toxicity. Applications of Enzone® are currently being made in California with an experimental use permit (EUP).

Exposure monitoring was conducted on workers handling Enzone® under the EUP. High performance liquid chromatography (HPLC) was used to detect 2-thiothiazolidine-4-

carboxylic acid (TTCA) in the urine samples. TTCA is a specific metabolite of CS_2 in *vivo* and has been used to estimate the absorbed dose of CS_2 for industrial hygiene monitoring. The analytical method was validated with the linearity of the calibration curve, the precision of the replicates, recovery of spikes and the long stability of the standard and samples. The recoveries of the field spiked urine samples averaged 88.7% with a standard deviation of 10.4%. The recovery of the TTCA laboratory spikes during the validation study combined with spiked samples from the long term stability experiment averaged 74.1% (SD 11.1%). Results from the storage stability study indicate that TTCA concentrations in urine were stable over a 30 day storage period. The results from the HPLC analysis of the urine specimens were multiplied by 0.16. This correction was necessary due to the reduced volume of the sample that was injected into the HPLC and the increase in concentration of the ether solution used to extract the TTCA. The TTCA results from analysis of the 48 urine specimens after the dilution correction ranged from 0.03 ppm to 0.64 ppm.

The ratio of the concentration of TTCA to the creatinine concentration in the urine was used to correlate exposure to CS_2. The LOD and LOQ for TTCA concentrations in the urine were estimated from calibration curve data obtained during the validation studies. Methanol solutions of TTCA at 0.2, 2.0, 20 and 200 ppm were analyzed with HPLC to generate the calibration curve data. The standard deviation (SD) from the results of the lowest concentration were calculated daily (39 samples) and a pooled standard deviation (SDp) was derived for the validation study. The SDp value was used to estimate the background level of TTCA present in urine which could not be detected. This value (0.022 ppm) was then increased by 3X and 10X to derive a LOD value at three standard deviations (0.07 ppm) and a LOQ at 10 standard deviations (0.22 ppm) above the SDp for TTCA. During the analysis of the urine specimens, the results were multiplied by 0.16 to correct for the reduction in the volume and increase in the concentration of the specimen analyzed. This correction was also applied to the LOD and LOQ values for TTCA calculated from the standard curve samples resulting in a LOD value of 0.011 ppm and LOQ of 0.035 ppm for TTCA in urine.

The ratio of the concentration of TTCA to the creatinine concentration in the urine was used to correlate exposure to CS_2 for the mixer/loader and the two applicators at each site. Urine specimens were collected from each worker prior/to the start of the application and after the application was completed. To generate a set of control urine samples, the study participants applied water from the nurse tanks into the irrigation system at each site 1-4 days before the sodium tetrathiocarbonate application was made. These control samples were used to quantify the TTCA/creatinine ratios present in urine that are the

result of exposure to CS_2 present in the environment and from the diet of the study participants. After the water application, the nurse tanks were filled with sodium tetrathiocarbonate and the applications were made with the active ingredient. The values for the TTCA and creatinine results from analysis of the urine specimens from the workers at the application sites (furrow, drip and sprinkler) were reported for the control applications, pre and post exposures, and the sodium tetrathiocarbonate application, pre and post application exposures. The TTCA to creatinine ratios were then calculated on a µmol/mmol basis with a correction in the TTCA values made for the field spike recovery rate of 88.7%. The corrected results as an arithmetic mean for the three sites were:
a. pre-water only control; 0.18 µmol/mmol (SD 0.13 µmol/mmol)
b. post-water only control; 0.15 µmol/mmol (SD 0.07 µmol/mmol)
c. post-water only control minus pre-water only control; -0.03 µmol/mmol) (SD 0.09 µmol/mmol)
d. pre-exposure sodium tetrathiocarbonate; 0.13 µmol/mmol (SD 0.13 µmol/mmol)
e. post-exposure sodium tetrathiocarbonate; 0.13 µmol/mmol (SD 0.13 µmol/mmol)
f. post-exposure sodium tetrathiocarbonate minus pre-exposure sodium tetrathiocarbonate; 0.01 µmol/mmol (SD 0.07 µmol/mmol)

The following mean ratios were compared for statistical differences using the Student's t-Test: a and d, a and b, d and e, and c and f. It was concluded there were no statistically significant differences between the means of the compared groups when the df = 16 and the alpha = 0.05. A non-parametric, Wilcoxon Signed Rank Test was used to compare the post-exposure sodium tetrathiocarbonate minus pre-exposure sodium tetrathiocarbonate ratios for each site to determine if the preponderance of positive values indicated an increase in the TTCA/creatinine ratio as a result of sodium tetrathiocarbonate exposure. The results indicate there is no significant difference between the paired pre- and post-sodium tetrathiocarbonate application values in the TTCA/creatinine ratio.

The statistical evidence indicates there was not a significant change in the TTCA/creatinine ratio during the study. This implies that the exposure to CS_2 from the application of sodium tetrathiocarbonate did not take place at levels that were detectable above the ambient ratio of TTCA/creatinine in the urine that is caused by environmental sources of CS_2.

To calculate an LOD for the TTCA/creatinine ratio in urine (µg/mg), the LOD for TTCA (0.011 ppm) and the mean value of 1156 ppm for creatinine from the analysis of the urine specimens, were used by the registrant. This value was converted to µmol/mmol to yield a LOD of 0.0065 for CS_2 exposure ([TTCA/creatinine] x 1000 x [molecular weight creatinine/molecular weight TTCA]). A Study by Campbell *et a/* (1985) determined the

relationship between the eight hour TWA exposure to CS_2 and the observed increase in the TTCA/creatinine ratio. The slope of the line plotted from the observations was calculated to have an increase of 1 µmol/mmol in the TTCA/creatinine ratio per 3.47 ppm exposure to CS_2 over an eight hour TWA period. The LOD for an eight hour TWA exposure to CS_2 was calculated as:

$$0.0065 \text{ X } 3.47 \text{ ppm } CS_2 \text{ TWA} = 0.022 \text{ ppm } CS_2 \text{ TWA}$$

The concentration of a gas measured in ppm can be converted to µg/L by the following formula:

µg/L = ppm x molecular weight/24.45 L (volume of one mole of gas at 25oC)

Therefore: µg/L = 0.022 ppm x 76.14/24.45 L = 0.067

This value can be used to estimate the absorbed daily dose from an eight hour exposure to CS_2 at the LOD level with a 50% absorption rate. A ventilation rate of eight liters per minute (Thongsinthusak et *al.*,1993) for eight hours times the concentration of carbon disulfide (0.067 µg/L) for a 58 kg woman is equivalent to a 2.2 µg/kg dose. This dose is several fold less than the "no significant risk level" (11 µg/kg) that has been recommended for Proposition 65 by RCHAS. **Based on the very low levels of occupational exposure to carbon disulfide, occupational exposures while handling sodium tetrathiocarbonate appear to be insignificant.**

III. Effect of Label Uses and Required Protective Clothing on Occupational Exposure

The registration of Enzone® on tomatoes represents a major new use that can incur exposure to a large population of growers and PCOs. The shank application method and the potential to treat up to 75 acres per day will incur exposures at levels likely to exceed those uses monitored in this study. The crop “tomatoes" has been deleted from the latest copy of the Enzone® label provided by the Pesticide Registration Branch. However, the shank or *ground injection* application method is still included on the label for applications to grapes and citrus. This method will incur greater occupational exposures to sodium tetrathiocarbonate and carbon disulfide for the applicator who must apply the material with a tractor. Shanks clog and collect debris that must be checked and cleaned by the applicator. These necessary activities will incur exposures that cannot be considered insignificant and must be mitigated in some manner, or the shank method of application can be deleted from the label.

IV. Non-Occupational Exposure to Carbon Disulfide

As a gas carbon disulfide has the potential to drift off the application site and expose persons living or working in areas adjacent to the treatment area. Two studies were conducted that included measurements of the concentrations of CS_2 that drifted off-site during and after the completion of a sodium tetrathiocarbonate application. Observations were made at 50 and 100 feet from the edge of the treatment site at various compass points with organic vapor monitors. Readings were taken at one and five feet above the ground for up to 120 hours after the start of the application.

In the study by Green (1987), levels of CS_2 and hydrogen sulfide were monitored on site and off-site during the application of sodium tetrathiocarbonate with various chemigation methods. The organic vapor monitors (3M model 3500) used to detect $CS2_2$ had a sensitivity to measure levels down to 0.01 ppm. When used according to directions, these monitors can measure a time weighted average (TWA) concentration of CS_2 for the sampling period. The monitors were hung from a set of three stakes. One stake was located in the center of the treatment site and two more stakes were placed 50 feet from the edge of the treatment area at the anticipated downwind and upwind locations. Pretreatment samples were taken on and off-site to observe the ambient levels of CS_2. An organic vapor monitor was activated and then sealed for shipment at each site to act as a control sample.

In the pretreatment samples, measurable CS_2 was found in 10 of the 24 monitors taken at the four sites with an average of 0.013 ppm for those testing unequivocally positive. At the drip irrigation application site, the blank monitor showed CS_2 contamination with the pretreatment sample results ranging from <0.01-1.4 ppm. Different monitors were then exposed during and after the sodium tetrathiocarbonate application for 8, 23 and 43 hours after the start of the application. At one site a four hour application of sodium tetrathiocarbonate was made at the maximum annual label rate of 100 gallons per acre with flood irrigation to treat 0.86 acres of oat stubble. During the trial the wind was observed to blow from the south at 3-7 mph and then from the northwest at 5-10 mph. The eight hour off-site samples observed the greatest concentrations of CS_2 with a mean value of 0.085 ppm (range 0.08-0.10 ppm). At a second site a drip application at eight gallons of sodium tetrathiocarbonate per acre (27% of maximum label rate) was made to 12 acres of grapes for four hours. During this trial the wind was observed blowing from the northwest at 5-7 mph. The highest levels of CS_2 were observed in the 32 hour samples with a mean value of 0.218 ppm (range 0.02-0.46 ppm). The contamination of the blank and the wide range of results for the pretreatment samples raises the question of integrity for these sample results. Two other sites monitored the drift from sodium

tetrathiocarbonate applications made with rainbird sprinklers and mini-sprinklers. However, chemigation with sprinklers is prohibited on the proposed Enzone® label and the off-site CS_2 exposure potential for these application methods was not considered.

A second study was conducted by Krieger *et a/.* (1992) to monitor the CS_2 levels resulting from a 100 gallon/acre application of sodium tetrathiocarbonate to one acre. The application was made with flood irrigation during a one hour period which is much faster than the recommended label rate. Stations were set up to observe the time weighted average (TWA) CS_2 concentrations at eight hour intervals. These stations monitored air levels of CS_2 at one and five feet elevations at nine different locations at the site. One station was located in the center of the application site and four other stations were placed in the north, east, west and south partitions of the treated area. An additional four sampling stations were placed 100 feet away from the edge of the treated area at the north, east, west and south partitions. During the 120 hour monitoring period, inversion weather conditions prevailed which should contribute to observing the maximum CS_2 air concentrations.

The limit of detection (LOD) for the analytical method used to detect CS_2 in air was 0.005 ppm. Readings that were below the LOD were assigned a value equal to one-half the LOD (0.0025 ppm). The results were corrected for recovery and reported during the first 48 hour period as 8 hour TWAs with the subsequent periods reported as 24 hour TWAs. The levels of CS_2 detected were consistently greater at the one foot elevation than the five foot elevation. For the purpose of estimating CS_2 concentrations in the breathing zone of workers, the five foot elevation observations are the most relevant. Concentrations of CS_2 were generally highest at the south on-site location where a pool of water formed during the application. The average TWA for the on-site levels of CS_2 during the first eight hours at five feet was 0.217 ppm and 0.236 ppm during the second eight hour period. After these readings the TWA values decline steadily to 0.013 ppm during the 72-96 interval. For the off-site levels at five feet, the average TWA for CS_2 during the first 24 hours were: 0-8 hours - 0.060 ppm, 8-16 hours - 0.036 ppm and 16-24 hours - 0.046 ppm.

The values observed in the second study were used to derive an estimate of the nonoccupational exposure to CS2 from applications of sodium tetrathiocarbonate. The five foot elevation data was used to estimate the CS_2 present in the breathing zone of active persons outside a dwelling or other structure that may provide protection from exposure. The highest CS_2 concentration (0.1 19 ppm) observed off-site at 0-8 hours after the application started can be converted to µg/L with the following equation.
µg/L = 1.00 ppm x molecular weight/24.45 L (volume of one mole of gas at 25°)

therefore: 0.119 ppm x 76.14124.45 = 0.37 µg/L

This value can be used to derive an estimate of the absorbed daily dose from an eight hour exposure to CS_2 with a 50% absorption rate. A ventilation rate of eight liters per minute (Thongsinthusak *et al.*, 1993) for eight hours times the concentration of CS_2 (0.37 µg/L) for a 58 kg woman is equivalent to a 12.3 µg/kg daily dose. This value is less than 1/1000 th of the NOEL of 22 mg/kg (inhalation) proposed by RCHAS for developmental toxicity. Exposure at this level would be exempt from the warning required by Proposition 65 for substances known to the State to cause reproductive toxicity. This conclusion is supported by observations made in the first study. At 50 feet from the application site, the highest concentration observed during the flood irrigation application of sodium tetrathiocarbonate was 0.10 ppm. This is equivalent to an absorbed daily dose of 10.6 µg/kg. **Based on the very low level of CS_2 found in ambient air following an application of sodium tetrathiocarbonate, the exposure appears to be insignificant.**

Attachments:

cc: John Donahue
Tian Thongsinthusak
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