STATE OF NEVADA
Department of Conservation & Natural Resources
DIVISION OF ENVIRONMENTAL PROTECTION
NEVADA DIVISION OF ENVIRONMENTAL PROTECTION
protecting the future for generations
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February 12, 2007

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Re. **BMI Plant Sites and Common Areas Projects, Henderson, Nevada**
NDEP Review of Human Health Toxicological Criteria, DMPT, DEPT dated January 16, 2007
Submitted by Syngenta Crop Protection

Dear Sirs and Madam:

The NDEP has completed a review of an electronic mail from Syngenta to the NDEP on the subject of Human Health Toxicological Criteria for DMPT and DEPT. The NDEP provides comments below:

Syngenta identified toxicological surrogates for dimethyl phosphorodithioate (CASRN 756-80-9) (DMPT) and diethyl phosphorodithioate (CASRN 298-06-6) (DEPT) in a report dated October 31, 2006 (Integral, 2006). The need for toxicological surrogates for DMPT and DEPT was identified by NDEP based on the lack of adequate dose-response data for these chemicals. This technical memorandum provides a response to Syngenta's proposal to modify the surrogate-based reference doses (RfDs) for DMPT and DEPT.

Based on structural similarity, physical/chemical properties, and the availability of chronic toxicity data, the Integral document identified the following toxicological surrogates:

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Chemical Requiring Surrogate	Toxicological Surrogate
DMPT (dimethyl phosphorodithioate)	Isopropyl methyl phosphonic acid (IMPA)
DEPT (diethyl phosphorodithioate)	Diisopropyl methyl phosphonate (DIMP)

As previously communicated (NDEP, 2006), NDEP concurs with the identification of the toxicological surrogate chemicals and the applicability of the RfDs for the identified surrogates for purposes of assessing potential upper bound health risks associated with DMPT and DEPT in environmental media at the BMI site. However, NDEP does not concur with the application of a "modifying factor" to the RfDs, which would increase the acceptable daily dose and risk-based soil concentrations by an order of magnitude. The basis of our position is provided below.

I. Uncertainties in the RfDs for the Surrogate Chemicals, the USEPA RfD Approach and the Toxicological Surrogate Approach

1. USEPA's Low Confidence in the RfDs

USEPA's confidence in the RfDs for both DIMP and IMPA is rated "low" (USEPA, 2007) due to limitations in the primary study and toxicity database for both chemicals. Low confidence indicates USEPA's judgment that the data supporting the RfD may be of limited quality and/or quantity and that additional information could result in a change in the RfD (USEPA, 1989, 1993).

2. USEPA's Identified Scientific Shortcomings of the RfD Approach

Although USEPA intends for the RfD estimates to be conservative, USEPA recognizes that there is considerable uncertainty regarding the RfDs. As described in Risk Assessment Guidance for Superfund (RAGS) (USEPA, 1989), the RfD is an estimate, " with uncertainty spanning perhaps an order of magnitude or greater". Specifically, USEPA has identified areas of scientific shortcomings regarding the traditional RfD approach, which include, but are not limited to (USEPA, 1993, 2002):

- The shape of the dose-response curve is not considered;
- The selection of the appropriate "adverse effect" may change as scientific knowledge increases and the correlation of precursor effects with toxicity becomes known;
- Guidelines have not yet been developed to take into account the reliability of studies in regard to the number of animals;
- A number of gaps in current testing protocols exist regarding life stage considerations;
- A number of gaps in the evaluation of endpoints included exist (e.g., functional evaluations are generally not integrated with structural evaluations);
- Generally, there is a lack of information on toxicokinetics; and

- An underlying assumption of the RfD is that the internal dose of the active form of an agent at the target site is the relevant measure of dose.

3. Uncertainties Regarding the Toxicological Surrogate Approach

It is generally recognized that using a toxicological surrogate approach for health risk assessment contributes to uncertainty in the risk characterization, even when specific toxicological mechanisms and/or structure-activity-relationships are understood. Although DMPT and DEPT are structurally similar to the proposed surrogates, the mechanism of action for DMPT and DEPT toxicity is unknown. Syngenta proposes a modifying factor based on the difference in electronegativity between P=O and P=S bonds. NDEP does not consider an approximation of relative electronegativity to be directly extrapolated to toxicity. Accordingly, the application of a modifying factor that implies the toxicities of DMPT and DEPT are 10-fold less than the toxicities of IMPA and DIMP, respectively, is not warranted.

II. Conclusions

NDEP concurs with the applicability of the RfDs for IMPA and DIMP for purposes of assessing potential upper bound health risks associated with DMPT and DEPT in environmental media at the BMI site. However NDEP does not endorse the application of a "modifying factor" to the surrogate-based RfDs, which would increase the acceptable daily dose and risk-based soil concentrations by an order of magnitude. This regulatory decision is based on the following considerations: (1) the low confidence in the dose-response databases and associated RfDs for IMPA and DIMP, (2) limitations identified by USEPA regarding the current RfD approach, (3) the uncertainties in the comparative toxicity of DMPT and DEPT and the identified surrogates, and (4) the lack of defensibility of extrapolating relative electronegativity to relative toxicity when mechanism of action is unknown.

Accordingly, for purposes of health risk assessments of DMPT and DEPT prepared for the NDEP, the RfDs for the toxicological surrogates should be applied without modification. If this methodology results in unacceptable risks for DMPT and/or DEPT, alternative risk characterization methodology and/or risk management goals will be considered by the NDEP.

III. References Cited

Integral Consulting, Inc. (Integral), 2006. Development of Human Health Toxicological Criteria for DMPT and DEPT. Prepared for Syngenta Crop Protection. October 31.

NDEP, 2006. **BMI Plant Sites and Common Areas Projects, Henderson Nevada**: *NDEP Review of Human Health Toxicological Criteria, DMPT, DEPT* dated November 1, 2006 Submitted by PES Environmental on behalf of Syngenta Crop Protection. November 27.

USEPA, 1989. Risk Assessment Guidance for Superfund, Vol. I, Human Health Evaluation Manual (Part A). Office of Emergency and Remedial Response. December. http://www.epa.gov/oswer/riskassessment/ragsa/index.htm

USEPA, 1993. Reference Dose (RfD): Description and Use in Health Risk Assessments. Background Document 1A, March 15. http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=22506

USEPA, 2002. A Review of the Reference Dose and Reference Concentration Processes. Risk Assessment Forum, December. http://www.epa.gov/iris/RFD_FINAL%5B1%5D.pdf

USEPA 2007. Integrated Risk Information System (IRIS). Online database of USEPA toxicity criteria. Website: www.epa.gov/iris/

NDEP believes that additional discussion is not warranted on this subject. Should you have any questions, please do not hesitate to contact me.

Sincerely,

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