STATE OF NEVADA
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Department of Conservation & Natural Resources
Allen Biaggi, Director
DIVISION OF ENVIRONMENTAL PROTECTION
Leo M. Drozdoff, P.E., Administrator

August 29, 2006

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Re. **BMI Plant Sites and Common Areas Projects, Henderson, Nevada**
Derivation of Toxicological Surrogate

Dear Sirs and Madam:

Attachment A contains the Nevada Division of Environmental Protection's (NDEP's) derivation of toxicological surrogates for dimethyl phosphorodithioic acid (DMPT) and diethyl phosphorodithioic acid (DEPT). The Companies must use these toxicological surrogates for DMPT and DEPT unless a suitable technical justification can be made to substantiate the use of a different surrogate.

If you have any questions, do not hesitate to contact me.

Sincerely,

Brian A. Rakvica, P.E.
Supervisor, Special Projects Branch
Bureau of Corrective Actions

BAR:s

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Robert Thompson, Drilling Supervisor, Division of Water Resources, 400 Shadow Lane, Suite 201, Las Vegas, NV 89106

Attachment A

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Technical Memorandum

To: Brian A. Rakvica, P.E.
Nevada Division of Environmental Protection (NDEP), Bureau of Corrective Actions

From: Teri Copeland, M.S., DABT and Joanne Otani Fehling, R.N., M.S.N., P.H.N.

Date: August 28, 2006

Re: Identification of Toxicological Surrogates for DMPT and DEPT

This technical memorandum provides a toxicity-based assessment to support the selection of toxicological surrogates, and associated toxicity criteria, for purposes of the assessment of potential noncancer toxicity and risk associated with oral exposure to the following organophosphate (OP) pesticides:

- dimethyl phosphorodithioate[1] (DMPT) (CASRN 756-80-9) and
- diethyl phosphorodithioate[2] (DEPT) (CASRN 298-06-6).

These pesticides are of interest to NDEP and have not been assigned a noncancer oral toxicity criterion by USEPA (2006) or ATSDR (2005).

I. Executive Summary

In response to a request from NDEP, toxicological surrogates were identified for DMPT and DEPT based on consideration of mechanism of action, structural similarity, parent compounds, and availability of relevant toxicity data. Data sources relied upon for the recommendations are identified in the text of this technical memorandum and full references, including online URLs, are provided in the references cited section.

DMPT and DEPT parent compounds (chemicals that are metabolized by humans to result in the formation of DMPT or DEPT in the body) were selected as toxicological surrogates, with multiple lines of support for the identification of the specific parent compound as the toxicological surrogate. For both DMPT and DEPT, the toxicological surrogates have been assigned oral reference doses by USEPA and were determined to be applicable for purposes of assessing potential noncancer risk associated with exposure to DMPT or DEPT, respectively.

A summary of the toxicological surrogates for DMPT and DEPT and the associated oral reference doses is provided below.

[1] Synonym: dimethyl phosphorodithioic acid.

[2] Synonym: diethyl phosphorodithioic acid.

Chemical Requiring Surrogate	Toxicological Surrogate	Oral Reference Dose (mg/kg-day)
DMPT (dimethyl phosphorodithioate)	dimethoate	0.0002
DEPT (diethyl phosphorodithioate)	phosalone	0.002

II. Mechanism of Action of Organophosphate Pesticides

Inhibition of the cholinesterase enzyme (ChE) is a biochemical mechanism common to all organophosphate (OP) pesticides (Amdur et al., 1991). Transmission of nerve impulses in the body requires the ChE enzyme. OP pesticides disable ChE, which can result in symptoms of neurotoxicity, including tremors, nausea, and muscular weakness at low doses and paralysis and death at higher doses. OPs have a similar mechanism of action in both insects and mammals, including humans, however the more toxic forms of OPs (i.e., the oxygen analog metabolites formed via oxidative desulfuration in both insects and mammals) are rapidly detoxified in mammals, but not in insects due to a lack of the detoxifying enzymes in insects. This mechanism is the basis for the species selectivity of OP pesticides.

At very low doses, OPs may cause some inhibition of ChE in mammals, including humans, without associated neurotoxicity. This phenomenon is supported by the fact that effect levels for ChE inhibition are generally lower than effect levels for neurotoxicity in mammalian species (Amdur et al., 1991; USEPA, 1998, FAO/WHO, 1997). The three primary tissues in which mammalian ChE data are monitored, for purposes of toxicological studies, are red blood cells, plasma, and brain. USEPA acknowledges that ChE inhibition is more accurately categorized as an exposure biomarker rather than a toxicological endpoint for *red blood cells and plasma*:

> "In the absence of clinical signs in humans or animals or the absence of morphological data in animals, the quantitative nature of the inhibition of red blood cells (RBC) and/or plasma cholinesterase inhibition is considered unreliable for assessing significant biological adverse changes, but can be used as a biomarker of exposure." (USEPA, 1998).

However, USEPA recommends that a noted decline in *brain* ChE should be evaluated by risk assessors in terms of possible effects that are biologically significant, and uses such data in setting or supporting reference doses (USEPA, 1998).

III. Selection of Toxicological Surrogate for DMPT

Identification of Toxicological Surrogate

Dimethoate (CASRN 60-51-5) was selected as the toxicological surrogate for purposes of characterizing potential noncancer risks (i.e., hazard quotients) for DMPT. This selection is supported by the following:

- Like DMPT, dimethoate is a dimethyl phosphorodithioate. Dimethyl phosphodithioates have two sulfur atoms bonded to the central phosphorus, one of which is a double bond, and two oxygens bonded to the central phosphorus, each also bonded to a methyl group (see Figure 1).

- DMPT is a chief metabolite of dimethoate in mammals (FAO/WHO, 1997) (Figure 1) and, similar to other OP pesticides, inhibits ChE (FAO/WHO, 1997; USEPA, 2006).

- As dimethoate is rapidly metabolized in the liver, it is likely that the cholinesterase inhibition reported following oral administration of dimethoate is due to activity of DMPT and metabolites of DMPT (FAO/WHO, 1997).

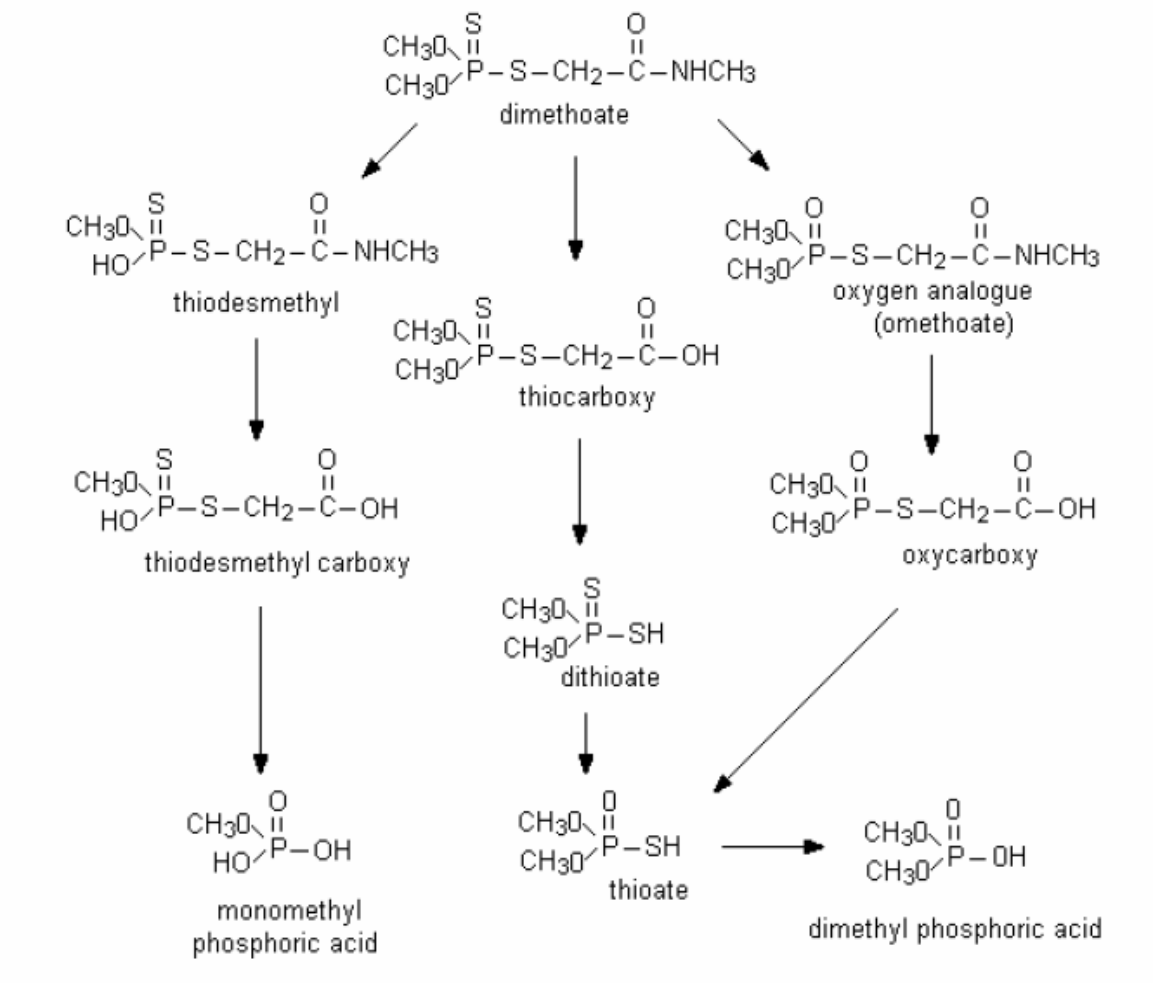

Figure 1: Metabolic Pathway for Dimethoate in Rats[3] (FAO/WHO, 1997)

Relevant Toxicity Criterion for Toxicological Surrogate for DMPT

USEPA has derived an oral reference dose (RfD) for dimethoate, based on animal and human data (USEPA, 2006). The RfD is defined by USEPA as "an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime" (USEPA, 2006). The oral

[3] Information provided in FAO/WHO (1997) for dimethoate indicates that metabolism of dimethoate is similar in humans and other mammals, including rats. Such similarities have also been shown for other OPs.

RfD for dimethoate is based on a rat No-Observed-Effect-Level (NOEL) for brain cholinesterase inhibition of 0.05 mg/kg-day (equivalent to approximately 1 ppm in the diet for two years) and an uncertainty factor (UF) of 300. The UF of 300 is based on the application of (1) a UF factor of 100 to account for interspecies (extrapolation from rat to human) and intraspecies (human variability) differences and (2) an additional UF of 3 to account for the lack of a chronic dog feeding study and rabbit teratology study. When the NOEL is divided by the comprehensive UF of 300, the resulting oral RfD is 2 E-4 mg/kg-day (0.0002 mg/kg-day). Because dimethoate is identified as a toxicological surrogate for DMPT, this RfD is identified as applicable to DMPT for purposes of assessment of potential chronic health risks to residential and occupational receptors using the USEPA CERCLA risk assessment framework (USEPA, 1989 and relevant supplements)[4].

IV. Selection of Toxicological Surrogate for DEPT

Identification of Toxicological Surrogate

Phosalone (CASRN 2310-17-0) was selected as the toxicological surrogate for purposes of characterizing potential noncancer risks (i.e., hazard quotients) for DEPT. This selection is supported by the following:

- Like DEPT, phosalone is a diethyl phosphorodithioate. Diethyl phosphodithioates have two sulfur atoms bonded to the central phosphorus, one of which is a double bond, and two oxygens bonded to the central phosphorus, each also bonded to an ethyl group (see Figure 2).

- DEPT is a chief metabolite of phosalone in humans (Vasilic et al., 1993) and, similar to other OP pesticides, inhibits ChE (Vasilic et al., 1993).

- Because phosalone is rapidly hydrolyzed in the body, its diethylphosphorus metabolites, including DEPT, are considered a more sensitive indicator of exposure in humans, as compared with the parent chemical (Vasilic et al., 1993).

- In addition to DEPT, there are two other chief metabolites of phosalone: diethyl phosphorothioate (DETP) and diethyl phosphate (DEP). DETP and DEP are direct metabolites of phosalone and are also metabolites of DEPT (i.e., DEPT is metabolized to DETP which is further metabolized to DEP) (Vasilic et al., 1993) (Figure 2).

- Based on the above, it is likely that the ChE inhibition reported following oral administration of phosalone is associated with DEPT and DEPT metabolites, which are the rapidly formed human metabolites of phosalone.

[4] USEPA has not assigned a dermal or inhalation RfD for dimethoate. Accordingly, extrapolation of the oral RfD to dermal and inhalation exposure pathways is an option that may be used for purposes of risk assessment of dimethoate and DMPT (USEPA, 2004). Uncertainties should be discussed when health risks are based on route extrapolation (USEPA, 1989).

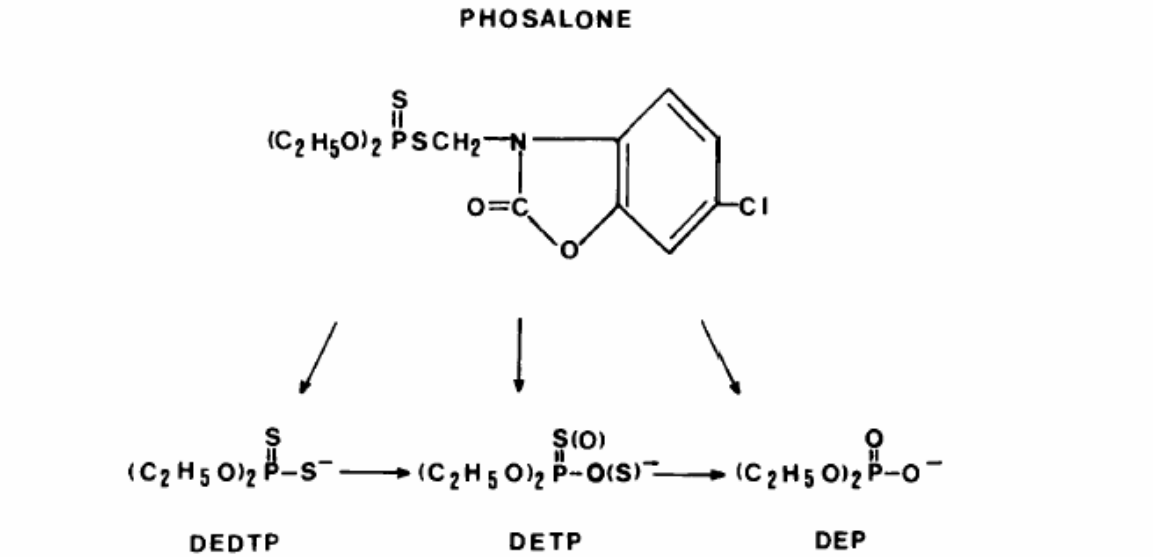

Figure 2: Metabolites of Phosalone in Human Serum and Urine (from Vasilic et al., 1993)

Relevant Toxicity Criterion for Toxicological Surrogate for DEPT

USEPA derived and posted an oral RfD online on 09/07/88 (USEPA, 2006). The current file on IRIS (USEPA, 2006) does not provide information as to that RfD, or its basis, but does note in the Revision History section of the current IRIS file that the RfD was withdrawn on 12/01/88. Although detailed information was not available via online search, the current IRIS file (USEPA, 2006) notes that on 08/01/95 EPA's RfD/RfC and CRAVE workgroups[5] were discontinued in May, 1995 and chemical substance reviews that were not completed by September 1995 were taken out of IRIS review at that time. It appears that phosalone was not included in subsequent IRIS peer review programs due to the fact that this pesticide was voluntarily withdrawn from US registration by the registrant, Rhone-Poulenc Ag Company in 1989 (USEPA, 2000). Based on information published by USEPA subsequent to the withdrawl of phosalone from the IRIS database (USEPA, 2000), withdrawl was not based on inadequate toxicity data.

As part of the Reregistration Eligibility Decision (RED) process, a Revised Human Health Risk Assessment was conducted by USEPA for phosalone (USEPA, 2000). In this document, USEPA states that "the acute and chronic dietary risk assessments are considered to be highly refined" (USEPA, 2000). Based on information provided in USEPA's 2000 Human Health Risk Assessment for phosalone, a chronic human RfD of 0.002 mg/kg-day was derived, based on a chronic oral rat No-Observed-Adverse-Effect-Level (NOAEL) of 0.2 mg/kg-day and a standard OP UF of 100 to account for interspecies (extrapolation from rat to human) and intraspecies (human variability) differences (USEPA, 2000). Because phosalone is identified as a toxicological surrogate for DEPT, this RfD is identified as applicable to DEPT for purposes of assessment of potential chronic health risks to residential and occupational receptors using the USEPA CERCLA risk assessment framework (USEPA, 1989 and relevant supplements)[6].

[5] These were earlier EPA peer-review groups.

[6] USEPA has not assigned a dermal or inhalation RfD for phosalone. Accordingly, extrapolation of the oral RfD to dermal and inhalation exposure pathways is an option that may be used for purposes of risk assessment of phosalone and DEPT (USEPA, 2004). Uncertainties should be discussed when health risks are based on route extrapolation (USEPA, 1989).

VI. References Cited

Agency for Toxic Substances and Disease Registry (ATSDR), 2005). Minimal Risk Levels (MTLs) for Hazardous Substances, December. www.atsdr.cdc.gov/mrls.html

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