UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

MEMORANDUM

DATE: June 24, 2008

SUBJECT: **Temephos:** Revised Registration Review Scoping Document for Human Health Assessments; PC Code: 059001; DP Number: D346600; Registration Review Case Number: 0006.

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Executive Summary

The Health Effects Division (HED) Temephos Registration Review Team has evaluated the status of the human health assessments for the organophosphate insecticide temephos to determine the scope of work necessary to support Registration Review. Temephos is a non-systemic organophosphate insecticide used as a mosquito, midge, and black fly larvicide for application to non-crop sites. It was first registered on July 9, 1965. Occupational handler exposures can be expected to occur from the registered uses of temephos which include swamps, ponds, wetlands, discarded tires, and tire piles. Occupational postapplication exposures are not expected to occur from the registered uses of temephos. Temephos currently has no residential uses.

The toxicity and exposure databases are adequate to support the risk assessments. Toxicity studies indicate that the inhibition of cholinesterase (ChE) is the most sensitive effect of temephos.

No risks of concern have been identified for dietary, drinking water or residential exposure. However, two occupational handler scenarios (applying granulars using fixed-wing aircraft and loading/applying granulars with belly grinder) remain a risk of concern. There is also one scenario (loading/applying granulars with a power backpack blower) that lacks exposure data that are needed to assess risk to temephos handlers. HED believes this scenario will not cause a risk of concern if appropriate PPE is worn (see discussion below regarding the use of granular temephos by loaders and applicators of back-pack blowers).

HED has recently reviewed a submission by Clarke Mosquito Control Products Inc. which included a label amendment (based on a submission of a 28-day dermal study) to reduce the current PPE requirements on nine end-use product formulations containing temephos insecticide that are registered for use as mosquito larvicide. HED's review (D346235, Oonnithan), discussed in more detail below, stated that:

- The non-cancer total short-, intermediate-, and long-term risk to mixers/loaders and applicators resulting from the use of liquid formulations of temephos are not of concern with the use of baseline PPE plus gloves. However, workers loading granular formulations of temephos must use baseline PPE plus gloves, coveralls, and a dust-mist respirator. In the high exposure scenarios involving treatment of tire piles, applicators are required to have additional PPE and engineering controls.

- The applicators who handle water soluble Basin-Bags™ containing temephos granules must wear basic PPE and chemical resistant gloves because of likely exposure to dust resulting from the formulation.

Introduction

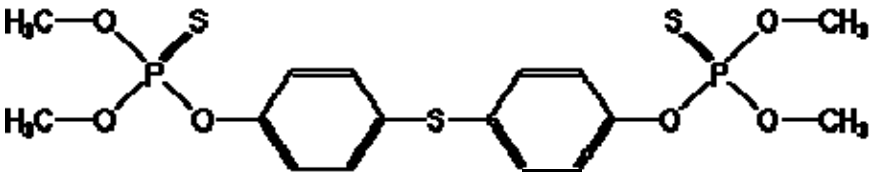
The Health Effects Division (HED) Temephos Registration Review Team has evaluated the status of the human health assessments for the organophosphate insecticide temephos to determine the scope of work necessary to support registration review. The team looked at the hazard and exposure databases for temephos to determine whether changes in science policy, newly available data or deficiencies in the databases *materially* affected the overall risk picture. The primary sources for the status update were HED and OPPIN databases and a search of the open literature using Google Scholar.

Temephos is a non-systemic organophosphate insecticide used as a mosquito, midge, and black fly larvicide for application to non-crop sites. It was first registered on July 9, 1965. Temephos currently has no established tolerances on food or animal commodities. Therefore temephos is currently considered to be a non-food use pesticide and a dietary assessment is not required. Temephos currently has no residential uses.

A drinking water risk assessment is not required for temephos because; 1) temephos is applied to water that cannot be used as a source of surface water/drinking water and 2) temephos is not expected to reach ground water that would be used for drinking water due to the short half-life of temephos.

Occupational handler exposures can be expected to occur from the registered uses of temephos which include swamps, ponds, wetlands, discarded tires, and tire piles. Occupational postapplication exposures are not expected to occur from the registered uses of temephos.

Chemical Identity

Table 1: Chemical Identity of Temephos	
Common Name(s)	Temephos, Phosphorothioic acid, Temefos
Chemical Class	Organophosphate, OP
IUPAC* Name	O,O,O′,O′-tetramethyl O,O′-thiodi-p-phenylene bis(phosphorothioate)
CAS** Name	O,O′-(thiodi-4,1-phenylene) bis(O,O-dimethyl phosphorothioate)
CAS Registry Number	3383-96-8
Chemical Formula	$C_{16}H_{20}O_6P_2S_3$
Chemical Structure	
*International Union of Pure and Applied Chemistry (IUPAC) **Chemical Abstract Service (CAS)	

Hazard Identification/Toxicology

The toxicology database for temephos has several data gaps. Most of the available studies were conducted in the 1960's and 1970's and do not meet the current requirements of Subdivision F Guidelines. However, the Agency has reviewed all toxicity studies submitted and has determined that available data are adequate to support the registration review of temephos for non-food, non-residential, low- volume, minor use.

Temephos is moderately toxic by the oral and dermal route, and has low toxicity via inhalation. Signs of toxicity observed in animals treated with high doses of temephos are typical of acute toxicity signs induced by cholinesterase inhibition (ChEI) which include; hypoactivity, labored breathing, rough coat, chromodacryorrhea, salivation, muscle spasms and tremors. Temephos is slightly irritating to eyes, but is not a skin irritant or a dermal sensitizer.

In subchronic toxicity studies in rats and dogs, the most sensitive toxicological endpoint is cholinesterase inhibition. Dose-related inhibition of plasma, red blood cell (RBC) and brain cholinesterase (ChE) activity occurs following repeated exposures of various durations. The severity of cholinergic symptoms correlates with the level of inhibition of plasma and RBC ChE activity. Rats are the most sensitive species to ChEI and male rats are the more sensitive sex. In rats, dietary temephos reduced plasma and RBC ChE activity at doses as low as 0.46 mg/kg. Dogs given 12.5 mg/kg of dietary temephos also had reduced plasma and RBC ChE activity. They also showed cholinergic symptoms

after 1 week of dosing which persisted throughout the 90-day study period. In addition to ChEI, the only other systemic effect in subchronic studies was decreased body weight gain in rats. This effect in rats, however, occurred at doses higher (17.5 mg/kg) than the dose which produced ChEI.

The Agency waived the developmental neurotoxicity studies for temephos when the generic organophosphate pesticide Data Call-In Notice (DCI) was released (August 6, 1999; 64FR42945-42047 and August 18, 1999; 64FR44922-44923) based on the low volume of use, the lack of food uses, and the low potential for any other exposure to children. At that time, it was also deemed that one study, the 21-day dermal toxicity in the rat with interim ChE measurements, would address three guideline studies (the acute and subchronic neurotoxicity studies and the 21-day dermal study). Since the completion of the RED in 2001, a 28-day dermal toxicity study with interim ChE measurements (MRID 47146802) was submitted to the Agency. This study has been reviewed and classified as Acceptable/guideline (TXR0054710, Yang).

Based on the temephos toxicity database, evidence of real increased susceptibility for developmental and reproductive factors of concerns cannot be determined with certainty. However, as described above, temephos has a low volume of use, currently has no food uses, and has low potential for any other exposure to children. As a result, HED does not believe that any developmental or reproductive toxicity studies should be required at this time. If the use pattern changes in the future (i.e., addition of residential or food uses) then the requirement of these studies would need to be reconsidered.

Temephos is not classified as a carcinogen although the available database to assess the carcinogenicity of temephos is limited. The only study available to examine the carcinogenicity of temephos is a 2- year chronic study in rats, in which the highest dose (15 mg/kg) did not induce tumor formation. In addition, several *in vitro* mutagenicity studies were examined and considered not adequate to evaluate the genotoxic potential of temephos. Because temephos is a non-food use pesticide and the occupational handler exposure duration is not chronic in nature, a chronic/ carcinogenicity study in another species is not required.

The available toxicology data for temephos are adequate to support the use pattern for the purpose of registration review with the exception of an immunotoxicity study, which is required to determine if temephos affects the immune system. This study was made a requirement recently in the new 40 CFR Part 158 toxicological data requirements.

Table 2: Summary of Toxicological Doses and Endpoints for Temephos for Use in Human Risk Assessments		
Exposure Scenario	**Toxicity Doses**	**Study and Toxicological Effects**
Acute Dietary (females 13-49 yrs) and General population	No registered food or residential uses; risk assessment is not required.	
Chronic Dietary (all populations)	No registered food or residential uses; risk assessment is not required.	
Dermal (all durations)	NOAEL = 3.0 mg/kg/day UF = 100 MOE of 100 is LOC	Rats, 28-day dermal study. Endpoint LOAEL of 50 mg/kg/day was based on inhibition of brain ChE in both sexes.
Inhalation (All durations)	NOAEL = 0.3 mg/kg/day Inhalation Absorption Factor 100% UF = 100 MOE of 100 is LOC	Rats, 90-day oral study. Endpoint LOAEL of 0.9 mg/kg/day was based on inhibition of red blood cell ChE and brain ChE in both sexes.
Cancer Classification	No tumors were observed in a carcinogenicity study in rats. Carcinogenicity study in mice not required for proposed non-food use.	

ChE = cholinesterase, LOAEL = lowest observed adverse effect level, LOC = level of concern, MOE = margin of exposure, NOAEL = no observed adverse effect level, UF = uncertainty factor.

Dietary Exposure and Risks

Temephos currently has no established tolerances on food or animal commodities. Therefore, temephos is currently considered to be a non-food use pesticide and a dietary assessment is not required.

A drinking water risk assessment is not required for temephos because; 1) temephos is applied to water that cannot be used as a source of surface water/drinking water and 2) temephos is not expected to reach ground water that would be used for drinking water due to the short half-life of temephos.

Residential Exposure and Risks

Temephos currently has no residential uses. Although temephos may be used in areas (e.g., temporary pools along the side of the road, standing water in discarded tires, and refuse piles) that may occasionally be visited by the general population, HED believes that it is unlikely that significant postapplication exposure would occur. This belief is based on the low application rate, the likelihood of a brief duration spent in such environments, and the probability of low exposure activities of the residents.

Aggregate Risk Assessment

Since there are currently no food or homeowner uses and drinking water exposure is not expected, an aggregate assessment is not required for temephos.

Occupational Exposure and Risks

HED believes that the potential occupational handler exposure routes for temephos are dermal and inhalation. Exposures may be of short-term (1 to 30 days) and intermediate-term (1 month to 6 months). In the temephos Phase-4 RED review (Becker, D240191, 09/27/1999), most scenarios were deemed to be below the Agency's level of concern based on the use of varying levels of PPE or engineering controls for all mixing, loading, and applying of temephos. Some potential risks of concern remained for two scenarios: applying granulars using fixed-wing aircraft and loading/applying granulars with belly grinder. One scenario (loading/applying granulars with a power backpack blower) also lacks appropriate exposure data that are needed to assess risk to temephos handlers. HED believes this scenario will not cause a risk of concern if appropriate PPE is worn (see discussion below regarding the use of granular temephos by loaders and applicators of back-pack blowers).

HED has recently reviewed a submission by Clarke Mosquito Control Products Inc. which included a label amendment (based on a submission of a 28-day dermal study) to reduce the current PPE requirements on nine end-use product formulations containing temephos insecticide that are registered for use as mosquito larvicide. HED's review (D346235, Oonnithan) recommended the following PPE statements for the liquid and granule product formulations of temephos:

<u>EC Formulations of Temephos Used on Wetlands (EPA Reg. Nos. 8329-60 and -69)</u>

- **Mixers, loaders, and ground applicators** must wear long-sleeved shirt, long pants, shoes, socks, and chemical resistant gloves.
- **Aerial applicators** must wear long-sleeved shirt and long pants, and shoes and socks.
- **Flaggers** must wear long-sleeved shirt and long pants, shoes and socks, and protective eyewear.
- **Engineering controls:** Pilots must wear chemical resistant gloves when entering or leaving an aircraft contaminated by pesticide residues. Used gloves must be stored in a closed chemical resistant container, such as a plastic bag, to prevent contamination of the inside of the cockpit.

<u>Granular Formulations of Temephos Used on Wetlands (EPA Reg. Nos. 8329-15, -16, -17, -57, - 70, and -71)</u>

- **Loaders of aerial equipment** must wear long-sleeved shirt and long pants, shoes and socks, chemical-resistant gloves, protective eyewear, and dust-mist respirator.
- **Loaders and applicators of back-pack blower** must wear coveralls over long-sleeved shirt and long pants, shoes and socks, chemical-resistant gloves, protective eyewear, and dust-mist respirator.
- **Aerial applicators** must wear long-sleeved shirt and long pants, shoes and socks, and use enclosed cockpits.
- **Flaggers:** must wear long-sleeved shirt and long pants, chemical-resistant foot wear plus socks, gloves, and protective eyewear.
- **Engineering controls**: Pilots must wear chemical resistant gloves when entering or leaving an aircraft contaminated by pesticide residues. Used gloves must be

stored in a closed chemical resistant container, such as a plastic bag, to prevent contamination of the inside of the cockpit.

- **Applicators applying water soluble Basin Bags™** (Reg. Nos. 8329-15, 16, and 17) must wear long-sleeved shirt and long pants, shoes and socks, and chemical-resistant gloves.

Granular Formulation of Temephos Used on Tires (EPA Reg. Nos. 8329-30)

- **Loaders of aerial equipment** must wear long-sleeved shirt and long pants, shoes and socks, chemical-resistant gloves, protective eyewear, and dust-mist respirator.
- **Loaders and applicators of back-pack blower** must wear coveralls over long-sleeved shirt and long pants, shoes and socks, chemical-resistant gloves, protective eyewear, and dust-mist respirator.
- **Aerial applicators** must wear long-sleeved shirt and long pants, shoes and socks, and use enclosed cockpits.
- **Flaggers:** must wear long-sleeved shirt and long pants, chemical-resistant foot wear plus socks, gloves, and protective eyewear.
- **Engineering controls**: Pilots must wear chemical resistant gloves when entering or leaving an aircraft contaminated by pesticide residues. Used gloves must be stored in a closed chemical resistant container, such as a plastic bag, to prevent contamination of the inside of the cockpit.

HED believes that postapplication exposures to temephos would be minimal based on the low application rate (0.5 lb ai/acre or less) of temephos, the short duration spent by the worker in a treated area (typically a few minutes), and the low exposure activity of the worker (typically dipping water from a temporary pool with a long handled dipper and examining the collected water for mosquito larvae).

Public Health and Pesticide Epidemiology Data

The temephos Phase-4 RED review (Becker, D240191, 09/27/1999) did not identify any cases of temephos related illness or injuries. In June 2008, HED searched the Office of Pesticide Programs' Incident Data System (IDS) from 2000 to present for incidents involving temephos, but still did not identify any cases of temephos related illness or injuries. This was attributed to the specialty use of this chemical for mosquito larvae control and due to the fact that the use is limited to use by public health officials and/or mosquito abatement districts or personnel under contract to these entities. For more information on the human health incident search please refer to the June 11, 2008 document, *Updated Review of Temephos Incident Reports*, in the temephos registration review docket.

Tolerance Assessment and International Harmonization

Temephos currently has no tolerances established under 40 CFR.

Environmental Justice

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. The Office

of Pesticide Programs (OPP) typically considers the highest potential exposures from the legal use of a pesticide when conducting human health risk assessments, including, but not limited to, people who obtain drinking water from sources near agricultural areas, the variability of diets within the U.S., and people who may be exposed when harvesting crops. Should these high exposures indicate potential risks of concern, OPP will further refine the risk assessments to ensure that the risk estimates are based on the best available information.

Cumulative Risk Assessment
Temephos was not considered in the organophosphate cumulative assessment because temephos has no residential uses, no food uses, and no residues of temephos are expected to occur in drinking water supplies.

Human Studies
Temephos risk assessments rely in part on data from studies in which adult human subjects were intentionally exposed to a pesticide or other chemical. These studies, which comprise the Pesticide Handlers Exposure Database (PHED), have been reviewed by the Agency and found on the basis of available evidence to have been neither fundamentally unethical nor significantly deficient relative to standards of ethical research conduct prevailing when they were conducted. There is no barrier in EPA's "Protection of Human Subjects" regulation to reliance on these studies.

Data Requirements
HED does not anticipate that additional residue chemistry, toxicology or occupational/residential exposure data will be required for the temephos registration review process, with the exception of the following outstanding studies listed below (See Tables 1-3 in Attachment 1 for more details):

- Storage stability of temephos technical product – 860.6317,
- Corrosion characteristics of temephos technical product – 860.6320, and
- Immunotoxicity Study – 870.7800.

References

Table 3: HED Memoranda Relevant to Registration Review			
Author	**Barcode/TXR #**	**Date**	**Title**
Nicole C. Paquette and Jonathan Becker	D260108	9/29/99	TEMEPHOS: Revised HED Chapter for the Reregistration Eligibility Decision (RED) Document
Jonathan Becker	D240191-3	9/27/99	Revised (Phase 4) Occupational and Residential Exposure Assessment and Recommendations for the Reregistration Eligibility Decision Document for Temephos
S. Oonnithan	D346235	2/20/08	Temephos: Request to Amend the Personal Protective Statements on the Labels of Abate® Formulations
Y. Yang	TXR0054710	10/02/07	Temephos Technical Grade: 28-Day Dermal Toxicity- Rat

Attachment 1

Table 1. Guideline Number: 860.6317 Study Title: Storage stability of temephos technical product
Rationale for Requiring the Data
The registrant is required in 40 CFR 158.310(e) to submit to the Agency basic information on the physical/chemical properties of the active ingredient.
Practical Utility of the Data
Data regarding stability will give some indication of the likelihood of chemical reactions during storage and use. This is basic information about the chemical which ensures chemical identity and is used to form the basis for labeling and product safety.

Table 2. Guideline Number: 860.6320 Study Title: Corrosion characteristics of temephos technical product
Rationale for Requiring the Data
The registrant is required in 40 CFR 158.310(e) to submit to the Agency basic information on the physical/chemical properties of the active ingredient.
Practical Utility of the Data
This is basic information about the chemical which ensures chemical identity and is used to form the basis for labeling and product safety.

Table 3. Guideline Number: 870.7800 Study Title: Immunotoxicity
Rationale for Requiring the Data
This is a new data requirement under 40 CFR Part 158 as a part of the data requirements for registration of a pesticide (food and non-food uses). The Immunotoxicity Test Guideline (OPPTS 870.7800) prescribes functional immunotoxicity testing and is designed to evaluate the potential of a repeated chemical exposure to produce adverse effects (i.e., suppression) on the immune system. Immunosuppression is a deficit in the ability of the immune system to respond to a challenge of bacterial or viral infections such as tuberculosis (TB), Severe Acquired Respiratory Syndrome (SARS), or neoplasia. Because the immune system is highly complex, studies not specifically conducted to assess immunotoxic endpoints are inadequate to characterize a pesticide's potential immunotoxicity. While data from hematology, lymphoid organ weights, and histopathology in routine chronic or subchronic toxicity studies may offer useful information on potential immunotoxic effects, these endpoints alone are insufficient to predict immunotoxicity.
Practical Utility of the Data
How will the data be used? Immunotoxicity studies provide critical scientific information needed to characterize potential hazard to the human population on the immune system from pesticide exposure. Since epidemiologic data on the effects of chemical exposures on immune parameters are limited and are inadequate to characterize a pesticide's

potential immunotoxicity in humans, animal studies are used as the most sensitive endpoint for risk assessment. These animal studies can be used to select endpoints and doses for use in risk assessment of all exposure scenarios and are considered a primary data source for reliable reference dose calculation. For example, animal studies have demonstrated that immunotoxicity in rodents is one of the more sensitive manifestations of TCDD (2,3,7,8-tetrachlorodibenzo-p-dioxin) among developmental, reproductive, and endocrinologic toxicities. Additionally, the EPA has established an oral reference dose (RfD) for tributyltin oxide (TBTO) based on observed immunotoxicity in animal studies (IRIS, 1997).

How could the data impact the Agency's future decision-making?

If the immunotoxicity study shows that the test material poses either a greater or a diminished risk than that given in the interim decision's conclusion, the risk assessments for the test material may need to be revised to reflect the magnitude of potential risk derived from the new data.

If the Agency does not have this data, a 10X database uncertainty factor may be applied for conducting a risk assessment from the available studies.