Health Canada Santé Canada

Evaluation Report for Category B, Subcategory 1.1, 7.0 Application

Application Number: 2014-5159
Application: New / Changes TGAI Prod Chemistry-New Source(site) same registrant
Reinstatement of Registered Product-Reinstatement of Registered Prod.
Product: Thimet MC-85 Technical Phorate
Registration Number: 19320
Active ingredients (a.i.): Phorate (PHR)
PMRA Document Number : 2550208

Purpose of Application

The purpose of this application was to reinstate Thimet MC-85 Technical Phorate based on new information.

Chemistry Assessment

Common Name: Phorate
IUPAC* Chemical Name: *O,O*-diethyl *S*-[(ethylsulfanyl)methyl] phosphorodithioate
OR
O,O-diethyl *S*-ethylthiomethyl phosphorodithioate
CAS† Chemical Name: *O,O*-diethyl *S*-[(ethylthio)methyl] phosphorodithioate

* International Union of Pure and Applied Chemistry
† Chemical Abstracts Service

Thimet MC-85 Technical Phorate has the following properties:

Property	Result
Colour and physical state	Colourless to pale yellow liquid
Nominal concentration	91.6%
Odour	Mercaptan-like
Density at 20°C	1.16 g/mL
Vapour pressure at 25°C	85.9 mPa
pH	3.7

Property	Result
Solubility in water at 25°C	50 mg/L
n-Octanol/water partition coefficient	Log K_{ow} = 3.92

The chemistry requirements for Thimet MC-85 Technical Phorate have been fulfilled.

Health Assessments

Toxicology Summary

A detailed review of the toxicological database for Thimet MC-85 Technical Phorate was previously conducted in 2002 and summarized in the Proposed Acceptability for Continuing Registration report PACR2003-01. For the current application to reinstate the registration of Thimet MC-85 Technical Phorate, additional toxicology data were received and are summarized below, as well as in Table 1 and 2 in Appendix 1. The assessment outlined below takes into account this newly submitted information within the context of the previously reviewed toxicity database reported in PACR2003-01. The toxicology endpoints for use in the human health risk assessment are summarized in Table 3 of Appendix I.

As described in PACR2003-01, phorate is highly acutely toxic in laboratory animals via the oral, dermal and inhalation routes. Following both single and repeated dosing with phorate, the most sensitive indicator of toxicity was the inhibition of cholinesterase (ChE), an enzyme necessary for the proper functioning of the nervous system, as well as associated clinical signs of cholinergic toxicity. Female animals were more sensitive than their male counterparts to the toxic effects of phorate, and the pregnant female was more sensitive than the non-pregnant female. Phosphorylated phorate metabolites (phorate sulfoxide and phorate sulfoxone) were of comparable toxicity to phorate. There was no evidence suggestive of delayed neurotoxicity and there was no evidence of histopathological effects on the central nervous system in any of the available studies. Phorate was not genotoxic, nor was it carcinogenic to either rats or mice. Phorate did not cause fetal malformations in rats or rabbits. In the rat and rabbit developmental toxicity studies, as well as in the rat reproductive toxicity study, reduced fetal/offspring viability was noted at doses that caused deaths in maternal animals. Although the developmental and reproductive toxicity studies did not demonstrate any sensitivity of the young animal relative to the adult animal, lack of cholinesterase measurements in these studies precluded a definitive assessment of this issue. On the basis of the available toxicity studies, phorate was anticipated to have a high dermal absorption potential. A notable feature of phorate was the steepness and potency of the dose–response following acute and short-term dosing. No-observed-adverse-effect-levels (NOAELs) were very close to dose levels that elicited mortality in the test animals. At the time of the PACR2003-01, it was noted that the toxicology database did not include a developmental neurotoxicity (DNT) study including comparative ChE assessments, a repeat-dose inhalation study or an assessment of neurotoxic esterase.

The following toxicology studies conducted in rats with phorate were received with the current application: DNT studies (range-finding and two definitive studies), which included comparative cholinesterase assays (CCA) in pregnant and lactating females, and in their offspring; CCAs following acute and repeat-dosing in juvenile and adult animals, as well as an assay to investigate time to peak effect (TTPE) for ChE inhibition following acute dosing; and a 4-week immunotoxicity study in adult females, which also included ChE measurements. Waiver requests were received for the repeat-dose inhalation study and the assessment of neurotoxic esterase. A suite of studies conducted with the phosphorylated phorate oxon metabolites (phorate oxon, phorate sulfone oxon and phorate sulfoxide oxon) was also received. These included TTPE CCAs in adult and juvenile rats, and dose tolerance studies in pregnant, juvenile and adult rats.

Acceptable ChE data were available in several of the newly submitted studies. Decreases in brain cholinesterase (BChE) and erythrocyte cholinesterase (EChE) activities were noted in adult females at the mid- and high-dose in the immunotoxicity study. In the range-finding DNT study, EChE and BChE activities were decreased in pregnant animals at the high-dose, and BChE activity was also decreased in maternal animals at the same dose during the lactation period. Effects on ChE activity were also noted in offspring in this study, including decreases in BChE activity at the mid- and high-doses for pups at post-natal day (PND) 11, and decreases in BChE and EChE activities at the high-dose for pups at PND 21. There were no treatment-related effects on fetal ChE activity (gestation day 20), nor was ChE activity inhibited in pups during the very early post-natal period (at PND 4).

Limitations with the ChE data were noted in the remaining newly submitted studies that measured ChE activity. For example, the assay designed to assess the TTPE for ChE inhibition following a single dose was unacceptable and not used in the assessment since ChE inhibition was not demonstrated at any of the doses tested, and therefore the TTPE could not be established. Also, in the single- and repeat-dose CCA, dose levels were insufficient to produce a clear cholinergic response and establish points of departure. It was also uncertain whether animals were sampled at the time of peak effect given the inadequacy of the supporting TTPE study. Consequently, the data from this study were not adequate to permit a quantitative comparison of age-related sensitivity, and were considered supplemental. In the definitive DNT studies, although effects on ChE activity were noted, the data did not lend well to statistical analyses/modeling due to an insufficient number of dose groups in either study. Despite these limitations, data from the range-finding DNT study were adequate to allow for a comparison of ChE inhibition between the pregnant and the young animal that had been exposed in utero, and also directly dosed during the post-natal period.

Benchmark dose analysis was conducted on ChE data for several critical studies to allow for a more accurate point of departure for risk assessment, as well as for a more direct comparison of the inhibitory effects of phorate on cholinesterase activities in the adult and the young animal. Maintaining its current approach for the interpretation of cholinesterase inhibition data, the PMRA has selected a benchmark response of 10% and 20% for BChE and EChE analysis, respectively, where applicable. Throughout the phorate database, there was a trend for BChE to be affected at lower doses compared to EChE. Benchmark dose analysis of BChE inhibition in the range-finding DNT study indicated that the young animal was not more sensitive than the pregnant animal following repeated dosing.

Two DNT studies were received with the current application. In the initial DNT study, the high-dose group had to be terminated due to excessive toxicity (clinical signs and death) in maternal animals and their offspring. There were no other treatment-related findings in maternal animals at the lower doses. In view of the excessive toxicity observed at the high-dose, a second study was conducted using a control and a single treatment group that employed a dose level falling between the mid- and high-dose of the initial study. Because of this, the results from these studies were examined together. In the second study, treatment-related findings in maternal animals were limited to decreased ChE activity. In the initial study, in addition to the effects on pup viability observed at the high-dose, decreases in BChE and EChE activities, as well as effects on neurobehavioural parameters, were noted in offspring at lower doses. The latter effects included increased motor activity in PND 21 pups and decreased acoustic startle response in PND 60 male pups, both of which were observed at the mid-dose. Differences between the control groups for the motor activity and acoustic startle response presented challenges when comparing the data from the two studies. However, the observation of similar trends for these neurobehavioural parameters at a higher dose in the second study supports these findings as being treatment-related. There were no apparent effects in maternal animals at the doses producing these effects in offspring, but limitations in the study precluded modeling of the ChE data. Benchmark dose analyses of the ChE data from the range-finding DNT study, however, provided evidence that BChE inhibition occurred in maternal animals at doses below those causing these neurobehavioural effects in offspring.

Decreases in brain morphometric measurements were observed in several brain regions of treated offspring in the second DNT study. These included decreases in measurements in the frontal and parietal cortex, hippocampus and folium pyramis of the cerebellum in PND 22 animals, and decreases in measurements in the cerebrum (length and width), hippocampus, corpus callosum and folium pyramis of the cerebellum in PND 62 animals. There were no apparent findings in the tissues that were examined at the mid-dose in the initial study, although not all of the areas affected by treatment in the second study (as noted above) were examined in the initial study. As noted above, due to early termination of the high-dose group in the initial study, no morphometric analyses were conducted at this dose level. For these reasons, it is difficult to draw definitive conclusions regarding the effect level for brain morphometric changes. However, given the observation of other findings (i.e., neurobehavioural effects) at the mid-dose in the initial DNT study, the missing morphometric information for these brain regions would not impact the overall endpoint selection.

Although there were no obvious treatment-related effects on learning and memory at any dose level in the DNT studies, there was limited confidence in these data due to issues with the particular methods that were used to conduct the M-maze test. These included failure to control for direction bias, use of a limited number of trials, and lack of clear criteria to assess learning. The additional reversal task that was included in the assessment was further compromised by the poor performance of control animals. In light of this, residual uncertainty remains regarding potential effects on learning and memory in the young animal.

In the 4-week immunotoxicity study, there was no evidence of effects on the immune system. It was determined that a short-term inhalation toxicity study would not further inform the risk assessment due to the fact that the endpoints of concern (i.e. neurological effects in the young animal) identified following oral dosing are not addressed in the typical design of a short-term inhalation toxicity study. It was also concluded that the potential for delayed neurotoxicity was adequately assessed on the basis of the available data, and therefore testing of NTE activity was no longer necessary.

New studies received on the phorate oxon metabolites included TTPE studies and an 11-day tolerance study, both of which were conducted in adult and young rats. A tolerance study in pregnant rats was also submitted, which included EChE measurements. In the repeat-dose tolerance and TTPE assays, clinical signs indicative of ChE inhibition, as well as mortality, were observed in adult and juvenile animals. These findings occurred at lower doses in the young animal, suggesting increased susceptibility of the young to the effects of the oxon metabolites. TTPE values ranged from 1-2 hours and 4-8 hours in adult males and females, respectively, and 4-8 hours in PND 11 pups for the various oxon metabolites. In the dose-tolerance gestational exposure study, all three oxon metabolites caused decreased EChE activity in pregnant animals (BChE not assessed). Clinical signs and mortality were also noted in this study, and the results suggested that the pregnant animal was more susceptible to the effects of these compounds. It was also noted that clinical signs and mortality occurred at lower doses with the oxon metabolites compared to phorate, suggesting that these compounds are of higher toxicity than the parent compound.

Incident Reports

Since April 26, 2007, registrants have been required by law to report pesticide incidents to the PMRA that are related to their products. In addition, the general public, medical community, government and non-governmental organizations are able to report pesticide incidents directly to the PMRA. As of May 5, 2015, no human or domestic animal incident reports involving phorate had been submitted to the PMRA.

According to information from the California Pesticide Illness Database, 12 phorate-related human incidents were reported in California during the period of 1992-2012, most of which were associated with agricultural uses of phorate. In these incidents, neurological symptoms were predominantly reported, including blurred vision, dizziness, nervousness, sleepiness, miosis, headache, trembling, weakness, fainting, and excessive salivation. Dermal (rashes and itchy skin) and gastrointestinal (nausea and vomiting) symptoms were also reported.

The above information regarding incident reports relating to phorate was considered in this evaluation and risk assessment.

PCPA Hazard Characterization

For assessing risks from potential residues in food or from products used in or around homes or schools, the *Pest Control Products Act* requires the application of an additional 10-fold factor to threshold effects to take into account completeness of the data with respect to the exposure of, and toxicity to, infants and children, and potential prenatal and postnatal toxicity. A different factor may be determined to be appropriate on the basis of reliable scientific data.

With respect to the completeness of the toxicity database as it pertains to the toxicity to infants and children, the database included developmental toxicity studies in rats and rabbits, a reproductive toxicity study in rats, and DNT studies in rats. Comparative assessments of ChE inhibition in adult and young rats were also available.

With respect to potential pre- and post-natal toxicity, decreased fetal/pup viability was observed at doses causing maternal deaths in the rat and rabbit developmental toxicity studies, the reproductive toxicity study, and the DNT studies. At non-lethal dose levels, offspring effects in the DNT studies included BChE and EChE inhibition, as well as increased motor activity and decreased acoustic startle response, with brain morphometric changes observed at the next higher dose. The BChE data from the range-finding DNT study suggested that the findings in offspring occurred in the presence of maternal toxicity. There were no apparent treatment-related effects on learning and memory in the DNT studies; however, there was some residual uncertainty in the assessment as a result of issues related to the particular methods used. Although there were some limitations noted with the CCA data, adequate data were available for the subpopulations of concern, which indicated that the young animal was not more sensitive to ChE inhibition than the pregnant animal on a repeat-dose basis.

Despite the limitations noted in the DNT studies and with the CCAs, the database is considered adequate for characterizing pre- and post-natal effects and determining susceptibility of the young. With regards to serious effects, as noted above, there was some residual uncertainty regarding potential effects on learning and memory. In addition, changes in brain morphometric assessments were noted at a higher dose than that resulting in other effects in the young animal, including decreased acoustic startle response. However, brain morphometric measurements were not fully assessed at this dose level. Although acoustic startle response is known to represent a reflex involving sensory and muscular systems, there is a cognitive component as well. A treatment-related alteration in acoustic startle response may manifest as a wide range of neurological effects in humans. Thus, there is residual uncertainty regarding the seriousness of this endpoint, namely how an effect on acoustic startle response following a single, or a repeated exposure, would manifest in humans. This residual uncertainty, as well as uncertainty relating to potential effects on learning and memory, will be addressed in the risk assessment by means of the PCPA factor. Concerns regarding the effects on acoustic startle response were tempered by the fact that these effects occurred in the presence of maternal toxicity. In view of all of these considerations, the PCPA factor was reduced to 3-fold.

Acute Reference Dose (ARfD)

To estimate acute dietary risk (1 day), the NOAEL for offspring toxicity of 0.033 mg/kg bw/day, obtained from the combined results of the DNT studies, was selected for risk assessment. At the LOAEL of 0.11 mg/kg bw/day, increased motor activity, decreased acoustic startle response, and ChE inhibition were observed in offspring. Although the NOAEL is from a study in which repeated dosing was employed, the possibility that the endpoint of acoustic startle response could have resulted from a single exposure cannot be ruled out, and therefore this endpoint is considered relevant to an acute risk assessment. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. As discussed in the PCPA Hazard Characterization section, the PCPA factor was reduced to 3-fold. **The composite assessment factor (CAF) is thus 300.**

The ARfD is calculated according to the following formula:

$$\text{ARfD} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{0.033 \text{ mg/kg bw}}{300} = 0.00011 \text{ mg/kg bw of phorate}$$

The ARfD provides a margin of 2000-fold to the NOAELs for mortality of pregnant females and their offspring (approximately 0.2 mg/kg bw/day).

Acceptable Daily Intake (ADI)

To estimate risk from repeated dietary exposure, the NOAEL for offspring toxicity of 0.033 mg/kg bw/day, obtained from the combined results of the DNT studies, was selected for risk assessment. At 0.11 mg/kg bw/day, increased motor activity, as well as decreased acoustic startle response and ChE activity were observed in offspring. This study addressed the endpoint of concern (neurological effects) in the most sensitive subpopulation (the young). Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. As discussed in the PCPA Hazard Characterization section, the PCPA factor was reduced to 3-fold. **The composite assessment factor (CAF) is thus 300.**

The ADI is calculated according to the following formula:

$$\text{ADI} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{0.033 \text{ mg/kg bw/day}}{300} = 0.00011 \text{ mg/kg bw/day of phorate}$$

The ADI provides a margin of 2000-fold to the NOAELs for mortality of pregnant females and their offspring (approximately 0.2 mg/kg bw/day).

Cancer Assessment

There was no evidence of carcinogenicity; therefore, a cancer risk assessment was not necessary.

Occupational Risk Assessment

Toxicological Endpoints

For assessing occupational risks for all durations from exposure via the dermal and inhalation routes, the combined results of the DNT data were deemed most relevant. No repeat-exposure inhalation toxicity study was available, and the available 28-day dermal toxicity study was not considered appropriate for endpoint selection as it did not assess the endpoint of concern in the sensitive subpopulation (i.e. neurological effects in the young animal). The DNT data identified increased motor activity, as well as decreased acoustic startle response and ChE activity at dose levels of 0.11 mg/kg bw/day and higher. The NOAEL was 0.033 mg/kg bw/day.

The target Margin of Exposure (MOE) for these scenarios is 300, which includes uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability. As the worker population could include pregnant and nursing women, it is necessary to afford adequate protection of the fetus which may be exposed via their mother, as well as to nursing infants who may be exposed through breast milk. In light of concerns identified in the PCPA Hazard Characterization section above, an additional factor of 3-fold was applied. The selection of this study and MOE is considered to be protective of all populations, including nursing infants and the unborn children of exposed female workers.

Food Residues

No new field trial or processing residue data for phorate in potatoes were submitted to support re-instatement of Thimet MC-85 Technical Product (Reg. No. 19320), or for the related submission to register the new end-use product Thimet 20-G. Previously reviewed residue data from field trials conducted in/on potatoes were reassessed in the framework of this petition. In addition, a processing study in treated potatoes was also reassessed to determine the potential for concentration of residues of phorate into processed commodities.

Exposure to residues of the oxon metabolites in food and drinking water is not a health concern given that:

- A plant metabolism study for potatoes, carrots and radishes showed oxon metabolites at trace levels.
- For potato and drinking water, phorate oxon was monitored by PDP and no residues were detected, although phorate oxon sulfoxide and phorate oxon sulfone were not monitored.
- The US Pesticide Data Program (PDP) monitored some commodities (e.g. green beans) for all oxon metabolites and no residues were detected.
- Based on the available monitoring data for phorate, which show no detects, the formation of oxon metabolites in water treatment facilities is unlikely.

Maximum Residue Limit(s)

The recommendation for maximum residue limits (MRLs) for phorate in potato commodities was based upon the previously submitted field trial data, and the guidance provided in the OECD MRL Calculator. MRLs to cover residues of phorate in/on potatoes and its processed

commodities are proposed as shown in Table 1. Residues in processed commodities not listed in Table 1 are covered under the proposed MRLs for the raw agricultural commodities (RACs). In addition, the risks from exposure to total phorate residues from treated crops (other than potatoes), at the MRL levels established in exporting countries, exceed PMRA's level of concern. Therefore, MRLs are being proposed for all non-registered uses in Canada at the quantitation limit of the Canadian Food Inspection Agency (CFIA) enforcement analytical method (0.008 ppm per analyte for a total of 0.024 ppm).

Table 1 Summary of Field Trial and Processing Data Used to Support Maximum Residue Limit(s) (MRLs)

Commodity	Application Method/ Total Application Rate (g a.i./100 m row)	PreHarvest Interval (days)	Residues[1] (ppm)		Mean Experimental Processing Factor	Currently Established MRL (ppm)	Recommended MRL[3] (ppm)
			Min	Max			
Potatoes	In-furrow 0-7 days after planting/ 21-32	89-143	<0.05	0.27[2]	Chips (0.19x); Granules/ flakes (2.2x)	None	Potatoes (0.2) Potato flakes (0.6) Potato granules (0.6) All food crops (other than those listed in this item) (0.024)

[1]Total phorate residues (phorate, phorate sulfoxide, phorate sulfone, phorate oxygen analog, phorate oxygen analog sulfoxide and phorate oxygen analog sulfone) determined as phorate oxygen analog sulfone.
[2] Total residues of phorate were greater than 0.2 ppm in only 1 of the 25 individual samples; furthermore 17 samples out of 25 contained no quantifiable residues.
[3] Residue definition for enforcement is phorate, phorate sulfoxide and phorate sulfone only.

Based on the dietary burden and residue data, finite residues of phorate are not anticipated in the meat, meat byproducts and milk of livestock.

Following the review of all available data, MRLs as proposed in Table 1 above are recommended to cover residues of phorate, phorate sulfoxide and phorate sulfone only. Residues of phorate in these commodities at the proposed MRLs will not pose an unacceptable risk to any segment of the population, including infants, children, adults and seniors.

Environmental and Value Assessments

Environmental and value assessments were not required for this TGAI application.

Conclusion

The Pest Management Regulatory Agency has completed an assessment of the information provided, and has found the information sufficient to support the reinstatement of the product Thimet MC-85 Technical Phorate.

List of Abbreviations

ADI	acceptable daily intake
a.i.	active ingredient
ARfD	acute reference dose
BChE	brain cholinesterase
BMD	benchmark dose
$BMDL_{10}$	lower confidence limit of the benchmark dose associated with a 10% response
$BMDL_{20}$	lower confidence limit of the benchmark dose associated with a 20% response
BMR	benchmark response
bw	body weight
bwg	bodyweight gain
CAF	composite assessment factor
CCA	comparative cholinesterase assay
ChE	cholinesterase
DNT	developmental neurotoxicity
EChE	erythrocyte cholinesterase
fc	food consumption
GD	gestation day
kg	kilogram(s)
LD	lactation day
LOAEL	lowest observed adverse effect level
mg	milligram(s)
MOE	margin of exposure
NOAEL	no observed adverse effect level
PChE	plasma cholinesterase
PCPA	*Pest Control Product Act*
PMRA	Pest Management Regulatory Agency
PND	postnatal day
TTPE	time to peak effect

Appendix I

Tables and Figures

Table 1 Additional Toxicology Data for Technical Phorate
(Effects are known or assumed to occur in both sexes unless otherwise noted; in such cases, sex-specific effects are separated by semi-colons. Organ weight effects reflect both absolute organ weights and relative organ to bodyweights unless otherwise noted)

Study Type/Animal/PMRA #	Study Results
Comparative cholinesterase study (gavage) Wistar rat (PND 11 and 21 pups, adults) PMRA# 2471563	Study considered supplemental; however some of the ChE data were adequate for BMD analyses. <u>Single dose</u> 0.2 mg/kg bw/day: ↓ PChE (PND 11 & PND 21 ♀s); ↓ BChE (PND 11 & 21 ♂s) **BChE** BMD_{10}/ $BMDL_{10}$ =0.197/0.157 mg/kg bw (PND 11 pups) <u>10-day repeat-dose</u> (adults only tested) 0.2 mg/kg bw/day: ↓ PChE (♀) No effects noted on EChE with single or repeated dosing.

Developmental neurotoxicity, Range-finding (gavage) Wistar rats PMRA #2471549	NOAELs and LOAELs were not established as this was a dose range-finding study; however, some of the ChE data were adequate for BMD analyses. **Maternal toxicity** Effects noted at 0.22 mg/kg bw/day included salivation (GD 11, 14-16, 19 & LD 7), ↓EChE (GD 20) & ↓BChE (GD 20 & LD 21) activity; ↓PChE (GD 20 & LD 21) occurred at ≥ 0.11 mg/kg bw/day. **BChE** BMD_{10}/ $BMDL_{10}$ = 0.041/ 0.0294 mg/kg bw/day (GD 20) = 0.0703/ 0.0389 mg/kg bw/day (LD 21) **EChE** BMD_{20}/ $BMDL_{20}$ = 0.181/0.133 mg/kg bw/day (GD 20) **Offspring toxicity** Effects noted at ≥ 0.11 mg/kg bw/day included ↓bw (PND 1-7) & ↓bwg (PND 1-4), ↓BChE activity (PND 11), ↓PChE (PND 21). **BChE** BMD_{10}/ $BMDL_{10}$ = 0.0789/ 0.0558 mg/kg bw/day (PND 11) = 0.112/0.05163 mg/kg bw/day (PND 21 ♂) **EChE** BMD_{20}/ $BMDL_{20}$ =0.191/0.1517 mg/kg bw/day (PND 21)
Developmental neurotoxicity (gavage) Wistar rats PMRA #2471543	**Maternal toxicity** NOAEL = 0.11 mg/kg bw/day LOAEL = 0.33/0.22 mg/kg bw/day (dose was decreased after 13 days of dosing due to excessive toxicity), based on mortality, clinical signs in surviving dams (tremors, high stepping gait, labored respiration, salivation & chromodacryorrhea), ↓bw, ↓bwg & ↓fc **Offspring toxicity** NOAEL = 0.033 mg/kg bw/day LOAEL = 0.11 mg/kg bw/day, based on ↑ motor activity (PND 21); ↓ mean peak amplitude in acoustic startle (PND 60 ♂s), ↓EChE activity (PND 21 ♂), ↓BChE activity (PND 21 ♂) **BChE** BMD_{10}/ $BMDL_{10}$ = 0.0437/0.0319 mg/kg bw/day (PND 21 ♂) Note: Only some of the ChE data were adequate for BMD analyses.

Developmental neurotoxicity (gavage) Wistar rats PMRA #2471546	Study considered supplemental NOAELs and LOAELs were not established since only one dose group (0.22 mg/kg bw/day) was included in the study. **Maternal toxicity** Effects noted at 0.22 mg/kg bw/day included ↓BChE, ↓EChE and ↓PChE activity on LD 21. **Offspring toxicity** Effects noted at 0.22 mg/kg bw/day included ↑motor activity (PND 13 ♂s & PND 17 ♀s), ↓EChE, ↓BChE, and PChE activities (PND 21), ↓ morphometric measurements in several brain areas; ↓bwg (PND 16-21 ♂s), ↓ mean peak amplitude in acoustic startle (PND 60 ♂s)
4-week immunotoxicity study (diet) Sprague Dawley rat (♀ only) PMRA# 2471551	NOAEL = 0.1 mg/kg bw/day LOAEL = 0.2 mg/kg bw/day based on ↓ EChE activity & ↓ BChE activity **BChE** BMD_{10}/ $BMDL_{10}$ = 0.154/0.1213 mg/kg bw/day **EChE** BMD_{20}/ $BMDL_{20}$ = 0.187/0.1305 mg/kg bw/day No evidence of immunotoxicity

Table 2 Summary Toxicology Data for Phorate Oxon Metabolites

(Effects are known or assumed to occur in both sexes unless otherwise noted; in such cases, sex-specific effects are separated by semi-colons. Organ weight effects reflect both absolute organ weights and relative organ to bodyweights unless otherwise noted)

Study Type/Animal/PMRA #	Study Results
11-day pilot/tolerance study (gavage) Sprague Dawley rat (adult, PND 11 pups) PMRA# 2471560	NOAELs and LOAELs were not established as this was a range-finding study. **Adult toxicity** (phorate oxon, phorate sufoxide oxon, phorate sulfone oxon) Effects noted at ≥ 0.3 mg/kg bw/day included clinical signs **Juvenile toxicity** (phorate oxon, phorate sufoxide oxon, phorate sulfone oxon) Effects noted at ≥ 0.1 mg/kg bw/day included clinical signs.

Time-to-peak effect study (gavage) Sprague Dawley rat (adult) PMRA # 2471558	NOAELs and LOAELs were not established since this was a TTPE study. **Phorate Oxon** Time-to-peak effect for ChE inhibition was 1 hour post-dose in ♂s and 4 hours post-dose in ♀s. Other effects noted at 0.6 mg/kg bw included tremors and pale spleen. **Phorate Sulfoxide Oxon** Time-to-peak effect for ChE inhibition was 2 hours post-dose in ♂s and 8 hours post-dose in ♀s. Other effects noted at 0.6 mg/kg bw included unsteady gait (♂) **Phorate Sulfone Oxon** Time-to-peak effect for ChE inhibition was 1 hour post-dose in ♂ and 4 hours post-dose in ♀s. Other effects noted at 1.0 mg/kg bw included mortality, unsteady gait and tremors.
Time-to-peak effect study (gavage) Sprague Dawley rat (PND 11 pups) PMRA # 2471553	NOAELs and LOAELs were not established since this was a TTPE study. **Phorate Oxon** Time-to-peak effect for ChE inhibition was 4-8 hours post-dose in both sexes. **Phorate Sulfoxide Oxon** Time-to-peak effect for ChE inhibition was between 4 and 5-6 hours post-dose in both sexes. Other effects noted at 0.25 mg/kg bw included mortality. **Phorate Sulfone Oxon** Time-to-peak effect for ChE inhibition was 8 hours post-dose in ♂s and 4 hours post-dose in ♀s.
Range-Finding Gestational exposure study (gavage) Sprague Dawley rat 4 mated ♀/group PMRA# 2471555	NOAELs and LOAELs were not established as this was a range-finding study. **Phorate Oxon** Effects noted at ≥ 0.1 mg/kg bw/day included ↓EChE activity and pale spleen. **Phorate Sulfoxide Oxon** Effects noted at ≥ 0.1 mg/kg bw/day included ↓EChE activity. **Phorate Sulfone Oxon** Effects noted at ≥ 0.1 mg/kg bw/day included slight ↓EChE activity.

Table 3 Toxicology Endpoints for Use in Health Risk Assessment for Phorate

Exposure Scenario	Study	Point of Departure and Endpoint	CAF[1] or Target MOE
Acute dietary	Developmental neurotoxicity study	NOAEL = 0.033 mg/kg bw/day Decreased acoustic startle response	300
	ARfD = 0.00011 mg/kg bw		
Repeated dietary	Developmental neurotoxicity study	NOAEL = 0.033 mg/kg bw/day Increased motor activity, decreased acoustic startle response, ChE inhibition in offspring	300
	ADI = 0.00011 mg/kg bw/day		
Dermal – all durations[2]	Developmental neurotoxicity study	NOAEL = 0.033 mg/kg bw/day Increased motor activity, decreased acoustic startle response, ChE inhibition in offspring	300
Inhalation – all durations[3]	Developmental neurotoxicity study	NOAEL = 0.033 mg/kg bw/day Increased motor activity, decreased acoustic startle response, ChE inhibition in offspring	300
Cancer	A cancer risk assessment was not required		

[1]CAF (composite assessment factor) refers to a total of uncertainty and PCPA factors for dietary assessments; MOE refers to a target MOE for occupational assessments

[2]Since an oral NOAEL was selected, a dermal absorption factor of 100% was used in a route-to-route extrapolation. (Acute oral and dermal toxicity data were similar, indicating a high degree of dermal absorption).

[3] Since an oral NOAEL was selected, an inhalation absorption factor of 100% (default value) was used in route-to-route extrapolation.

References

A. List of Studies/Information Submitted by Registrant

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2471532 2014, Preliminary Analysis of THIMET Phorate, DACO: 2.13 CBI

2471533 2014, Physical and Chemical Properties of THIMET Phorate, DACO: 2.14

2471535 2014, Product Identity Data for Phorate Technical, DACO: 2.0

2471538 2014, Product Identity and Composition and Discussion of Formulation Impurities of THIMET Phorate, DACO: 2.11.4

2531622 2015, Manufacturing Summary and Detailed Production Process Description for Thimet MC-85 Technical Phorate Insecticide, DACO: 2.11.1,2.11.3 CBI

2531623 2015, Materials Used for Production ofThimet MC-85 Technical Phorate Insecticide, DACO: 2.11.3 CBI

2529153 2015, Phorate Plant Metabolism as Determined in the Scientific Literature, DACO: 6.3

2529168 2015, Phorate Crop Rotational Study Following OPPTS Guideline 860.1900, DACO: 7.4.4

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2471549 2004, BAS 225 I (Phorate) - Range finding developmental neurotoxicity study in Wistar rats; Oral administration to the dams and pups (gavage), DACO: 4.5.14

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2471555 2012, Phorate oxon, phorate sulfoxide oxon or phorate sulfone oxon: dose range-finding gestational exposure study in the Crl:CD(SD) rat by oral administration, DACO: 4.8

2471558 2012, Phorate oxon, phorate sulfoxide oxon or phorate sulfone oxon: single dose time to peak effect oral gavage study in young adult Crl:CD(SD) rats by clinical observations and cholinesterase analysis, DACO: 4.8

2471560 2012, Phorate oxon, phorate sulfoxide oxon or phorate sulfone oxon: Pilot/tolerance study in young adult and juvenile Crl:CD(SD) rats by oral gavage administration, DACO: 4.8

2471563 2004, BAS 225 I (phorate) - Study of the effects on cholinesterase levels in juvenile and young adult Wistar rats (age sensitivity) oral administration (gavage), DACO: 4.8

2536135 2015, Phorate Canadian Data Waiver Requests, DACO: 4.3.6,4.5.10

B. Additional Information Considered

i) Published Information
Human and Animal Health

PMRA Document Number	Reference
2552322	2015, Phorate Data from California Pesticide Illness Query Database (1992-2012), DACO: 4.8

ii) Unpublished Information
Human and Animal Health

PMRA Document Number	Reference
779011	2003, Methylazoxy Methanol Acetate – Positive Control Developmental Neurotoxicity Study in Wistar Rats – Single Intraperitoneal Administration to the Dams, DACO 4.5.12

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