Evaluation Report ERC2010-02

Tetrakis (Hydroxymethyl) Phosphonium Sulfate

(publié aussi en français)

17 February 2010

This document is published by the Health Canada Pest Management Regulatory Agency. For further information, please contact:

Publications
Pest Management Regulatory Agency
Health Canada
2720 Riverside Drive
A.L. 6605C
Ottawa, Ontario
K1A 0K9

Internet: pmra.publications@hc-sc.gc.ca
healthcanada.gc.ca/pmra
Facsimile: 613-736-3758
Information Service:
1-800-267-6315 or 613-736-3799
pmra.infoserv@hc-sc.gc.ca

Canada

HC Pub: 091171

ISBN: 978-1-100-14320-0 (978-1-100-14321-7)
Catalogue number: H113-26/2010-2E (H113-26/2010-2E-PDF)

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Overview

Registration Decision for Tetrakis (hydroxymethyl) Phosphonium Sulfate

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act* and Regulations, has granted conditional registration for the sale and use of the technical product Tolcide P75S, containing the active ingredient tetrakis (hydroxymethyl) phosphonium sulfate, and the end-use products Tolcide PS200 to control microbial slime formation in oilfield operations and in evaporative cooling towers and Tolcide PS75LT to control microbial slimes in oilfield operations.

An evaluation of available scientific information found that, under the approved conditions of use, the product has value and does not present an unacceptable risk to human health or the environment.

Although the risks and value have been found acceptable when all risk reduction measures are followed, the applicant must submit additional scientific information as a condition of registration.

This Overview describes the key points of the evaluation, while the Science Evaluation provides detailed technical information on the human health, environmental and value assessments of Tolcide 75PS and the end-use products Tolcide PS200 and Tolcide PS75LT.

What Does Health Canada Consider When Making a Registration Decision?

The key objective of the *Pest Control Products Act* is to prevent unacceptable risks to people and the environment from the use of pest control products. Health or environmental risk is considered acceptable[1] if there is reasonable certainty that no harm to human health, future generations or the environment will result from use or exposure to the product under its proposed conditions of registration. The Act also requires that products have value[2] when used according to the label directions. Conditions of registration may include special precautionary measures on the product label to further reduce risk.

To reach its decisions, the PMRA applies modern, rigorous risk-assessment methods and policies. These methods consider the unique characteristics of sensitive subpopulations in humans (for example, children) as well as organisms in the environment (for example, those most sensitive to environmental contaminants). These methods and policies also consider the

[1] "Acceptable risks" as defined by subsection 2(2) of the *Pest Control Products Act.*

[2] "Value" as defined by subsection 2(1) of the *Pest Control Products Act*: "the product's actual or potential contribution to pest management, taking into account its conditions or proposed conditions of registration, and includes the product's *(a)* efficacy; *(b)* effect on host organisms in connection with which it is intended to be used; and *(c)* health, safety and environmental benefits and social and economic impact."

nature of the effects observed and the uncertainties when predicting the impact of pesticides. For more information on how the PMRA regulates pesticides, the assessment process and risk-reduction programs, please visit the Pesticides and Pest Management portion of Health Canada's website at healthcanada.gc.ca/pmra.

What is Tetrakis (Hydroxymethyl) Phosphonium Sulfate?

Tetrakis (hydroxymethyl) phosphonium sulfate is a slimicide which provides effective prevention of microbial slimes in process waters against a range of slime-forming microbes. Tetrakis (hydroxymethyl) phosphonium sulfate acts primarily to increase the permeability of the outer membrane of the microbial cell envelope which causes protein and other cellular materials to be rapidly released from the cells. In addition, tetrakis (hydroxymethyl) phosphonium sulfate inhibits the sulfate reduction process within sulfate reducing bacteria.

Tolcide PS75 is a technical product containing 75% tetrakis (hydroxymethyl) phosphonium sulfate. Tolcide PS75 is used to manufacture the end use products Tolcide PS75LT and Tolcide PS200. Tolcide PS75LT is used to control microbial slime formation in oilfield operations. Tolcide PS200 is used to control microbial slimes in evaporative cooling towers and in oilfield operations.

Tolcide PS200 was proposed for use in pulp and paper processing facilities. Workers in the pulp and paper processing facilities may be exposed to mist downstream of the site of application. No data were submitted for the characterization of the level of worker exposure to mist and to tetrakis (hydroxymethyl) phosphonium sulphate and its by-products in pulp and paper facilities. Therefore, a risk assessment for this scenario could not be conducted and the use in pulp and paper processing facilities was not accepted to appear on the Tolcide PS200 label.

Health Considerations

Can Approved Uses of Tetrakis (Hydroxymethyl) Phosphonium Sulfate Affect Human Health?

Tetrakis (hydroxymethyl) phosphonium sulfate is unlikely to affect your health when used according to label directions.

Exposure to tetrakis (hydroxymethyl) phosphonium sulfate may occur when handling and applying the products. When assessing health risks, two key factors are considered: the levels where no health effects occur and the levels to which people may be exposed. The dose levels used to assess risks are established to protect the most sensitive human population (for example, children and nursing mothers). The risk assessment is conducted to ensure that the level of human exposure is well below the lowest dose at which effects occurred in animal tests. Only those uses where exposure is well below levels that cause no effects in animal testing are considered acceptable for registration.

Toxicology studies in laboratory animals describe potential health effects from varying levels of exposure to a chemical, and identify the dose where no effects are observed.

The technical product Tolcide PS75 was of high toxicity when given as a single oral dose to rats, and was of slight toxicity after a single dose was inhaled. It also caused eye and skin irritation in animals, and is considered to be a potential skin sensitizer. Consequently, the statements "Danger Poison", "Eye and Skin Irritant", and "Potential Skin Sensitizer", as well as the skull and crossbones symbol, are required on the label. The end-use products Tolcide PS75LT and Tolcide PS200 are considered to have the same acute toxicity profile as Tolcide PS75, and therefore the same statements and symbols will be required on the labels of Tolcide PS75LT and Tolcide PS200.

Tolcide PS75 was found to be genotoxic in some studies, and also to cause cancer in the uterus and adrenal gland. Health effects in animals given daily doses of Tolcide PS75 over longer periods of time included effects on the liver, lung, testes, uterus and bone marrow, as well as lymphoid depletion of spleen and thymus. Some animals died when higher doses of Tolcide PS75 were given, or when Tolcide PS75 was given for longer periods of time. There was no indication that Tolcide PS75 caused damage to the nervous system. When Tolcide PS75 was given to pregnant animals, effects on the developing fetus were generally observed at doses that were also toxic to the mother, which suggests that the fetus is not more sensitive to Tolcide PS75 than the adult animal. There were limitations with the study that tests for reproductive effects, therefore, the study was considered to be unacceptable for use in assessing human risk of Tolcide PS75.

A complete toxicology data package was not submitted to support Tolcide PS75, therefore, the hazard characterization for this chemical could not be completed. As the exposure was determined to be negligible based on the products use in cooling towers and oilfields, no further studies were required in order to complete the current assessment. However, for any future use expansions, the PMRA will reconsider the need to address these data concerns.

Residues in Water and Food

Dietary risks from food and water are not of concern.

Based on the use pattern for tetrakis (hydroxymethyl) phosphonium sulfate, dietary risk from food and water are not of concern.

Occupational Risks From Handling Tolcide PS200 and Tolcide PS75LT

Occupational risks are not of concern when Tolcide PS200 and Tolcide PS75LT is used according to label directions, which include protective measures.

A qualitative risk assessment conducted for individuals handling Tolcide PS75LT or Tolcide PS200 products, indicated that the risk for adults is not of concern when these products are used according to label directions.

Workers mixing, loading and applying Tolcide PS75LT or Tolcide PS200 can come in direct contact with tetrakis-hydroxymethyl phosphonium sulfate on the skin or through inhalation. Therefore, the label will specify that workers must wear coveralls over long sleeved shirt and long pants, chemical resistant gloves, socks, chemical resistant footwear, a respirator and goggles or a face shield when mixing, loading, and applying Tolcide PS75LT or Tolcide PS200, or during cleanup and repair.

Environmental Considerations

What Happens When Tetrakis (Hydroxymethyl) Phosphonium Sulfate is Introduced into the Environment?

Tetrakis (hydroxymethyl) phosphonium sulfate is toxic to freshwater alga and freshwater invertebrates, therefore, label instructions are required to protect these organisms and to minimize exposure to the aquatic environment.

Tetrakis (hydroxymethyl) phosphonium sulfate may enter the environment after it is used as a slimicide in oilfield operations and evaporative cooling towers. Tetrakis (hydroxymethyl) phosphonium sulfate is not persistent in water and is rapidly mineralized into carbon dioxide.

Tetrakis (hydroxymethyl) phosphonium sulfate is not expected to be present in air. Based on the use pattern, very little is anticipated to reach the environment and once there it rapidly transforms into carbon dioxide so is not expected to be persistent. Tetrakis (hydroxymethyl) phosphonium sulfate has limited potential to partition into sediment or organic matter and is non-persistent in the aquatic system. Under actual use conditions, tetrakis (hydroxymethyl) phosphonium sulfate residues were found to be below the detection limit (0.5 mg a.i./L) at the point of discharge into the watercourse. Tetrakis (hydroxymethyl) phosphonium sulfate residues are not expected to enter the soil and is, therefore, not expected to be found in the terrestrial environment.

Tetrakis (hydroxymethyl) phosphonium sulfate presents a low risk to mysid shrimp, fish, eastern oyster, and vascular plants. Tetrakis (hydroxymethyl) phosphonium sulfate is expected to adversely affect daphnids and freshwater green alga. Therefore, specific instructions on its toxicity to aquatic organisms and to minimize exposure to the aquatic environment are provided on the product labels.

Value Considerations

What is the Value of Tolcide PS75LT and Tolcide PS200?

Tolcide PS75LT controls microbial slime formation in oilfield operations. Tolcide PS200 controls microbial slimes in evaporative cooling towers and in oilfield operations.

Tolcide PS75LT and Tolcide PS200 provide effective prevention of microbial slimes in process waters against a range of slime-forming microbes. These products are compatible with current slime-management practices in oilfield operations and evaporative cooling towers. These products provide an alternative biocide for industrial process waters with a completely new chemistry, and are valuable alternative biocides in industries where the common practice is to regularly alternate slimicides.

Measures to Minimize Risk

Labels of registered pesticide products include specific instructions for use. Directions include risk-reduction measures to protect human and environmental health. These directions must be followed by law.

The key risk-reduction measures being proposed on the labels of Tolcide PS200 and Tolcide PS75LT to address the potential risks identified in this assessment are as follows.

Key Risk-Reduction Measures

Health
To avoid direct contact with Tolcide PS75LT or Tolcide PS200, loading and transfer is permitted only with a closed system. In addition, anyone handling this product must wear all the personal protective equipment stated on the labels.

Environment
As tetrakis (hydroxymethyl) phosphonium sulfate is toxic to freshwater algae and freshwater invertebrates, specific instructions to minimize exposure to the aquatic environment are provided on the product labels.

What Additional Scientific Information is Being Requested?

Although the risks and value have been found acceptable when all risk-reduction measures are followed, the applicant must submit additional scientific information as a condition of registration. More details are presented in the Science Evaluation of this Evaluation Report or in the Section 12 Notice associated with these conditional registrations. The applicant must submit the following information within the time frames indicated.

Chemistry

The following studies are required to complete the chemistry database for this product:

- Oxidizing and reducing properties of Tolcide PS75LT.
- Storage stability data of Tolcide PS200 stored at ambient temperature for one year.

Environment

- Representative chromatograms of unfortified and fortified surface and drinking water samples generated from the analysis of tetrakis (hydroxymethyl) phosphonium sulphate as well data demonstrating linearity of the ion chromatographic method used to determine tetrakis (hydroxymethyl) phosphonium sulphate in drinking and surface water are required for the residue methods. This study should be submitted within one year of the granting of this conditional registration.

- Develop and validate analytical methodology for tetrakis (hydroxymethyl) phosphonium sulphate and its transformation products using aquatic plant and animal tissues (preferably fish or bird tissue, but mammal tissues are also acceptable). The studies should be conducted using non-labelled tetrakis (hydroxymethyl) phosphonium sulphate and transformation products. Tissue samples should be spiked with the non-labelled compounds, extracted and subsequently analysed. Validation data should include precision, accuracy, recovery, LOQ and linear range. These studies should be submitted within one year of the granting of this conditional registration.

Value

The following studies are required to ensure that the lowest effective rates are being used:

- Operational trials are needed to determine the appropriate frequency of application in the oilfield water flooding and evaporative recirculating cooling tower uses. (Studies to be completed and submitted within one year of the conditional registration being granted).

Other Information

As these conditional registrations relate to a decision on which the public must be consulted,[3] the PMRA will publish a consultation document when there is a proposed decision on applications to convert the conditional registrations to full registrations or on applications to renew the conditional registrations, whichever occurs first.

The test data cited in this Evaluation Report (i.e. the test data relevant in supporting the registration decision) will be made available for public inspection when the decision is made to convert the conditional registrations to full registrations or to renew the conditional registrations (following public consultation). If more information is required, please contact the PMRA's Pest Management Information Service.

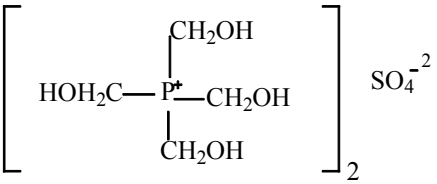
[3] As per subsection 28(1) of the *Pest Control Products Act.*

Science Evaluation

Tetrakis (hydroxymethyl) phosphonium sulfate

1.0 The Technical Grade Active Ingredient, its Properties and Uses

1.1 Identity of the Technical Grade Active Ingredient

Active substance	Tetrakis (hydroxymethyl) phosphonium sulfate
Function	slimicide
Chemical name	
1. International Union of Pure and Applied Chemistry (IUPAC)	bis[tetrakis(hydroxymethyl)phosphonium] sulfate (salt)
2. Chemical Abstracts Service (CAS)	Phosphonium, tetrakis(hydroxymethyl), sulfate
CAS number	55566-30-8
Molecular formula	$C_8H_{24}O_{12}P_2S$
Molecular weight	406.3
Structural formula	
Purity of the technical grade active ingredient	75% nominal (limits: 73.0–77.0%)

1.2 Physical and Chemical Properties of the Active Ingredients and End-Use Product

Technical Product — Tolcide PS75

Property	Result
Colour and physical state	Colourless liquid
Odour	Aldehyde-like
Melting range	Not applicable
Boiling point or range	108.5°C
Density	1.392 g/mL
Vapour pressure at 20°C	26.7 mm Hg
Henry's law constant at 20°C	2.76×10^{-14} atm m^3/ mole
Ultraviolet (UV)—visible spectrum	No absorption maxima above 300 nm.
Solubility in water at 20°C	Tolcide PS75 is an aqueous solution. It is fully miscible with water
Solubility in organic solvents at 20°C (g/100 mL)	Not determined
n-Octanol–water partition coefficient (K_{ow})	log $K_{ow} < 0$
Dissociation constant (pK_a)	pK_a = 5.18
Stability (temperature, metal)	Stable for 14 days at 54°C Unstable to aluminium, iron and tin powder

End-use Product—Tolcide PS75LT and Tolcide PS200

Property	Result	
End-Use Product	Tolcide PS75LT	Tolcide PS200
Colour	Colourless	Clear and colourless
Odour	Aldehyde-like	Odourless
Physical state	Liquid	Liquid
Formulation type	Solution	Solution

Property	Result	
End-Use Product	Tolcide PS75LT	Tolcide PS200
Guarantee	75% nominal (limits: 73.0–77.0%)	20% nominal (limits: 19.4–20.6%)
Container material and description	High density polyethylene (HDPE)	High density polyethylene (HDPE)
Density	1.38	1.0922
pH of 1% dispersion in water	3.19	3.2
Oxidizing or reducing action	Not an oxidizer or reducing agent; Some effect on zinc and iron. Requested clarifications of the reducing properties of the end-use product.	The test material has significant reducing capability.
Storage stability	The product is shown to be stable at ambient temperature for one year	Not determined. The storage stability data were requested for Tolcide PS200
Explodability	The product is not explosive. It is an aqueous solution	The product is not explosive. It is an aqueous solution

1.3 Directions for Use

Tolcide PS75LT and Tolcide PS200 are broad-spectrum slimicides that are effective against general heterotrophic and sulfate reducing bacteria. These products are used in oilfield water flooding operations, in which they are added to the injection system either immediately before or after the de-aerator. The products are generally used at rates to maintain a biofilm-free system (see Table 1.3.1).

In addition to the oilfield use, Tolcide PS200 is used in evaporative cooling towers at rates and frequencies (see Table 1.3.1) to prevent slime formation. The product is injected into the water system at a point which ensures efficient mixing.

Table 1.3.1 Microbial Slime Control Claims for Tolcide PS75LT and Tolcide PS200.

Site	Dose	Application Rate/L of process fluid			Frequency
		mg a.i./L	mg PS75LT/L	mg PS200/L	
Oilfield Water Flood	initial	up to 250	up to 330	up to 1250	for 1 to 3 hours
	maintenance	up to 40	up to 55	up to 200	continuously
Evaporative Cooling Towers	maintenance	19–100	—	95–500	up to 4 times daily

1.4 Mode of Action

Tetrakis (hydroxymethyl) phosphonium sulphate acts primarily to increase the permeability of the outer membrane of the microbial cell envelope. This increased permeability causes protein and other cellular material to be rapidly released from the cell. In addition, the sulfate reduction process within the sulfate reducing bacteria (SRB) is inhibited.

2.0 Methods of Analysis

2.1 Methods for Analysis of the Technical Grade of Active Ingredient

The methods provided for the analysis of the active ingredient and its impurities in Tolcide PS75 have been validated and assessed to be acceptable for the determinations.

2.2 Method for Formulation Analysis

The method provided for the analysis of the active ingredient in the formulations has been validated and assessed to be acceptable for use as an enforcement analytical method.

2.3 Methods for Residue Analysis

An ion chromatography method is used for the specific determination of tetrakis (hydroxymethyl) phosphonium sulphate in surface and drinking water. The method fulfilled the requirements with regards to accuracy and precision at the respective method limit of quantitation. Acceptable recoveries (70–120%) were obtained in surface and drinking water. Methods for residue analysis are summarized in Appendix I, Table 1.

3.0 Impact on Human and Animal Health

3.1 Toxicology Summary

The PMRA conducted a detailed review of the toxicological database for the active ingredient tetrakis (hydroxymethyl) phosphonium sulphate. Tetrakis (hydroxymethyl) phosphonium sulphate was tested using the technical product Tolcide PS75, which is an aqueous solution

containing 75% active ingredient. Doses reported below have been corrected for tetrakis (hydroxymethyl) phosphonium sulphate content. For all studies that were conducted via the oral route, the test substance was delivered via gavage. Studies conducted by the National Toxicology Program (NTP) were submitted in fulfillment of the requirement for rodent chronic/carcinogenicity data. These studies were conducted with B6C3F1 mice and Fischer F344 rats, while the majority of remaining toxicology studies were with Sprague-Dawley rats. Results from several short-term oral range-finding studies were included in the submitted NTP report. Although many of these range-finding studies are considered to be supplemental (as they did not fulfill all guideline requirements), they have been incorporated in the toxicology summary, as collectively, they provide further information regarding the hazard characterization of Tolcide PS75.

The absorption, metabolism and excretion of Tolcide PS75 was investigated in Sprague-Dawley rats using uniformly labelled (^{14}C)-tetrakis (hydroxymethyl) phosphonium sulfate, administered by gavage at single doses of ~1 or 50 mg/kg bw. Absorption was rapid (within 2 hours), while elimination from blood and plasma was slower (half lives of ≤3 and ≤8 days in plasma and blood, respectively). Some pharmacokinetic parameters were noted to be affected by dose. At the high dose, absorption was decreased compared to the low dose. In addition, high dose males demonstrated a slower rate of elimination and greater distribution than females, while at the low dose, pharmacokinetics were similar between the sexes. Primary excretion routes included urine (12–31% at 24 hours) and feces (4–37% at 24 hours). Expiration in air was noted (up to 13% after 2 days), but there were difficulties in capturing (^{14}C)-tetrakis (hydroxymethyl) phosphonium sulfate in air traps, and the possibility remains that as much as 30% may actually be expired in air (based on ~30% unaccounted radioactivity in a 7-day study). There was little retention in tissue (5%) after 7 days; however, distribution data were not available and, therefore, target tissues could not be identified. Tetrakis (hydroxymethyl) phosphonium sulfate appeared to be extensively metabolized. Nine metabolites were detected in urine, seven of which were also detected in feces, while no parent compound was detected in either urine or feces. The major metabolite was trishydroxymethyl phosphine oxide in both urine (~10% of administered dose) and feces (14–24% of the administered dose). The remaining eight metabolites were not positively identified in the submitted studies, leaving some uncertainty with regards to the metabolic pathway. The study authors hypothesized that formaldehyde was released at several steps along the metabolic pathway.

Tolcide PS75 was highly acutely toxic via the oral route, of low toxicity via the dermal route, and of moderate toxicity via the inhalation route. Tolcide PS75 was considered to be corrosive to the eye and was a dermal sensitizer. Tolcide PS75 was also considered to be irritating to the skin based on the necrosis of the eyelids observed in the eye irritation study, as well as irritation observed in the acute dermal toxicity study, dermal sensitization study (during induction phase), and the 28-day irritation study.

Acute toxicity data for Tolcide PS75 were referenced for the two end-use products. Therefore, the acute toxicity profiles for Tolcide PS200 (containing 20% tetrakis (hydroxymethyl) phosphonium sulfate) and Tolcide PS75LT (containing 75% tetrakis (hydroxymethyl) phosphonium sulfate) are as described above for Tolcide PS75.

In a short-term (28-days) dermal range-finding study conducted in the Sprague-Dawley rat, irritation (slight to severe) and decreased body weight gain and food consumption were observed at all doses tested. Irritation increased in severity with increasing duration and dose. At doses of 190 mg/kg bw/day tetrakis (hydroxymethyl) phosphonium sulfate or higher, animals were euthanized after four days of treatment due to the severity of the dermal reactions observed.

In short- and long-term oral studies, the liver was identified as the primary target organ of toxicity. Liver findings were consistently observed in the repeat dosing studies in rats (both Sprague-Dawley and Fischer F344) and in mice, and were noted to appear following ≥4 weeks of dosing. However, it should be noted that more subtle liver effects may not have been detected in the 2–4-week studies since histopathological examinations were not conducted. The predominant findings were liver enlargement and increased weight as well as vacuolation of hepatocytes. In the multigeneration reproduction study, bile duct proliferation and focal necrosis were also observed in the livers of parental animals. Effects on body weight were not consistently observed in the repeat-dose studies. In some short-term studies, body weight decrements were observed at doses as low as 5 mg/kg bw/day (90-day oral study with Fischer rat); however, in chronic studies conducted with mice and Fischer rats, there were no apparent effects on body weight at doses up to 10 mg/kg bw/day (highest dose tested). Clinical signs of toxicity noted at sublethal doses following repeated dosing included piloerection, emaciated appearance, salivation, diarrhea, rough coat and red-brown coat staining. In oral studies conducted with Fischer rats and mice, tremors (rat) and loss of hindlimb movement (both species) were noted in 14-day studies at high doses (≥100 mg/kg bw/day), while lymphoid depletion of the spleen and bone marrow hyperplasia were noted in the 90-day rat study.

Long-term oral studies were conducted with mice and Fischer rats by the NTP. Only two doses were tested in these studies (5 and 10 mg/kg bw/day). In mice, treatment-related findings included bone marrow hyperplasia, hematopoiesis of the liver, lymphoid depletion of the thymus, and focal atrophy of the spermatogenic epithelium. In rats, lymphoid depletion of the spleen and thymic cortex, as well as liver pathology were also observed. In both species, dilatation of the uterus and lung findings (congestion or edema) were noted. Effects were observed at the low dose in both chronic studies, and thus a no-adverse-effect level (NOAEL) could not be determined for either study. Limitations were noted in both studies, including the fact that only two doses were tested, NOAELs could not be established, several required parameters were not assessed (for example, organ weights and clinical chemistry), and significantly decreased survival was observed in male rats. These limitations may need to be reconsidered in the event that future expansion of the use pattern for tetrakis (hydroxymethyl) phosphonium sulphate involve chronic exposure scenarios.

Treatment-related deaths were observed in several repeat-dose studies of short- and long-term duration. In the 28-day dermal study in rats, all animals that received ≥190 mg/kg bw/day were euthanized due to severe irritation at the test site (following 4 days of treatment). In 14-day rat and mouse studies, deaths were observed at ≥100 mg/kg bw/day, while in a 28-day oral study, all rats that received 45 mg/kg bw/day of the test substance were killed in extremis following 20–22 days of treatment. In 90-day studies with mice and Fischer rats, there were deaths at ≥40 and 60 mg/kg bw/day, respectively. Mortalities also occurred in maternal animals in the two range-finding developmental toxicity studies at doses of 60 mg/kg bw/day (rabbit) and

68 mg/kg bw/day (rat). In the multi-generation reproduction study, there were treatment-related deaths at 12 mg/kg bw/day for P generation females (three of these associated with dystocia), and for F_1 generation animals of both sexes (during the pre-mating phase). In the NTP chronic studies, there was decreased survival in male rats at 5 and 10 mg/kg bw/day.

Treatment-related neoplastic lesions were noted in both the chronic rat and mouse studies. In female rats and mice, there was an increased incidence of endometrial stromal polyps at the high dose (10 mg/kg bw/day). In male mice, there was an increased incidence of adrenal pheochromocytomas at the high dose, as well as an increase in hyperplasia of the adrenal medulla, which is known to be difficult to distinguish from the neoplastic lesion (i.e. pheochromocytoma) during histopathological examination (Greaves et al., 1990, as cited in Smith, 2006). These studies suggest that Tolcide PS75 has carcinogenic potential.

Genotoxicity studies were conducted to evaluate the mutagenic and genotoxic potential of Tolcide PS75. In several of these studies, not all guideline requirements were met, and thus certain studies were considered to be supplemental. No evidence of mutagenic potential was observed in vitro with the Ames Bacterial Mutation Test or in an unscheduled DNA synthesis assay with rat hepatocytes. However, strains used to detect cross-linking agents were not included in the submitted Ames study, and the unscheduled DNA synthesis assay was considered unacceptable due to several deficiencies (including insufficient sample size and inadequate positive controls). Under the conditions of an in vitro mammalian cell gene mutation assay (cultures of thymidine kinase ± mouse lymphoma L5178Y cells), Tolcide PS75 was considered to be mutagenic. Colony size distribution assessments in the mammalian gene mutation assay revealed that colonies were predominantly smaller relative to negative controls groups, suggesting that Tolcide PS75 may induce gross chromosomal aberrations, rather than point mutations. This finding was consistent with the positive results observed in the in vitro chromosomal assay using Chinese hamster ovary cells. In an in vivo study, Tolcide PS75 did not induce micronuclei in a mouse micronucleus assay. A dominant lethal study was also submitted. This study was considered supplemental as the standard dosing regime was not followed. Furthermore, the results were considered to be inconclusive as an increase in post-implantation loss was observed at week 2 post-dosing (at 15 mg/kg bw/day, the highest dose tested), but not at week 1 post-dosing. Based on the data presented, which included positive results for chromosome aberrations, and limitations in several studies in which negative results were observed, Tolcide PS75 was considered to have genotoxic potential.

In light of the evidence of carcinogenicity in the animal bioassays and the positive results observed in the genotoxicity assays, it would be considered appropriate to use a linear low-dose extrapolation approach for a cancer risk assessment.

No neurotoxicity studies were submitted in support of this toxicology database. However, in the 90-day oral toxicity study conducted with Sprague-Dawley rats, a neurological assessment was carried out on all animals before the start of treatment, and on control and high dose groups during weeks 5 and 13. This neurological testing did not reveal any treatment-related effects. Some findings which can be considered to be indicative of neurotoxicity were noted in the 14-day studies conducted by the NTP. These included tremors, noted in Fischer rats, and hindlimb paralysis, observed in both rats and mice. However, as these findings occurred at lethal doses (≥100 mg/kg bw/day), they were more likely reflective of severe systemic toxicity, and thus not considered to signal concern for neurotoxic potential.

Developmental toxicity was investigated in rats (Sprague-Dawley) and rabbits. In both species, there was evidence of effects on the developing fetus. These effects included eye malformations in both species, and limb and cardiac malformations in rabbits. Malformations were only observed in two fetuses in the rat study, while the incidence of malformations and variations was much higher in rabbits. An increased incidence of skeletal variations (primarily extra thoraco-lumbar ribs) was also observed in fetuses of both species. There was some evidence of a dose-related increase in post-implantation loss in the rabbit study. However, concern for this finding on its own was not high since the increases did not achieve statistical significance, and the incidence at all dose levels was within the historical control range from studies conducted at the same laboratory. In rats, evidence of maternal toxicity (clinical signs, and gastrointestinal and liver lesions) was observed at a lower dose level than the noted developmental effects. In rabbits, maternal toxicity (including body weight loss and decreased food consumption) was observed at the same dose level as the developmental findings.

Reproductive toxicity was investigated in a 2-generation reproduction study conducted with Sprague-Dawley IGS rats. Effects in parental animals from both generations included slight decreases in body weight, liver findings, and mortalities. Liver toxicity was evidenced by increased liver weight and histopathological lesions (periportal hepatocyte enlargement and vacuolation in both generations, accompanied by bile duct proliferation and focal necrosis in the F_1 generation). There was an increase in mortality in P generation high dose females (three deaths in this group associated with dystocia), while in the F_1 generation, an increase in mortality was noted in both sexes at the high dose. In the P generation, effects were also noted in the adrenal gland (hypertrophy and increased weight) and uterus (dilatation). Lung findings (pneumonitis and pleuritis) were noted in parental animals from the F_1 generation. At the high dose (P generation), results suggestive of an effect on the reproductive system included the dystocia observed in three females, as well as a possible decrease in oocyte numbers. In parental animals, a no-effect level for systemic toxicity was established at the lowest dose tested (0.78 mg/kg bw/day).

A higher than usual number of offspring deaths was noted in the control group in the first generation of the reproduction study. Information submitted by the applicant provided evidence that these deaths may have been related to a strain-specific sensitivity to diet; however, this high background incidence of deaths potentially confounded the interpretation of the findings in this study. There was also conflicting information in some of the reported results which, combined with the confounding deaths in controls, yielded low confidence in the study results for reproductive success/offspring viability. Notwithstanding the unusual background incidence of

pup deaths, there was an apparent increase in pup mortality especially noted prior to postnatal day 1 in the high dose group (accompanied by decreases in live birth index, and mean litter size and weight). Due to the methods used in the study, it was not possible to distinguish whether these mortalities were stillbirths, or whether they occurred following delivery. These offspring findings, coupled with the dystocia and possible decreased oocyte count in parental animals, suggest an effect on reproductive fitness and offspring viability at the high dose in the first generation. In the second generation, background incidences of pup deaths were more within expected ranges; however, there was an increased number of deaths prior to postnatal day 1 at all dose levels compared to controls. Although these increases did not follow a dose-responsive trend, due to the issues with the quality of the data they cannot be dismissed and are considered to signal concern for possible reproductive/offspring effects. Concern for reproductive/offspring effects was heightened by other effects noted in developing fetuses in the Tolcide PS75 database. These included, malformations and variations in rats and rabbits, and suggestions of increased post-implantation losses in the rabbit developmental toxicity and rat dominant lethal studies. Overall, the limitations and uncertainties identified in the reproduction study call the validity of the study into question, and as such, the study has been determined to be unacceptable.

It is noted that there is potential for exposure to formaldehyde with use of the tetrakis (hydroxymethyl) phosphonium sulphate products. Formaldehyde is present as an impurity in the Tolcide 75PS technical product and associated end-use products. In addition, there is potential for formaldehyde to be released as a breakdown product of tetrakis (hydroxymethyl) phosphonium sulphate.

Several studies were conducted with trishydroxymethyl phosphine oxide, which is a major mammalian metabolite of tetrakis (hydroxymethyl) phosphonium sulphate, and also a degradate of tetrakis (hydroxymethyl) phosphonium sulphate in aqueous environments. Trishydroxymethyl phosphine oxide was found to be of low acute toxicity via the oral route. In a 28-day dermal study, signs of dermal irritation were noted at the lowest dose tested (300 mg/kg bw/day), which increased in incidence and/or severity with increasing dose. Evidence of systemic toxicity was noted at the highest dose tested (1000 mg/kg bw/day), and included effects on clinical chemistry parameters and the adrenal gland. Several genotoxicity studies were conducted, including a gene mutation assay in bacterial cells, and in vitro tests for gene mutations in bacterial and mammalian cells, and chromosomal aberrations in mammalian cells. Results from all of these tests were negative; however, it should be noted that the bacterial gene mutation test was not considered to be acceptable for several of the strains of bacteria that were tested, and thus the results cannot be considered conclusive for these strains. Further, this assay did not include strains that detect cross-linking agents, and thus the results from this test do not rule out the possibility that trishydroxymethyl phosphine oxide causes cross-linking mutations.

A bacterial gene mutation study was also conducted with a tetrakis (hydroxymethyl) phosphonium sulphate paper leachate, which contained a mixture of tetrakis (hydroxymethyl) phosphonium sulphate, trishydroxymethyl phosphine oxide and other residues. Results were negative from this test, indicating that this mixture does not induce mutations in the bacterial cells tested; however, the test was not considered acceptable for three of the five bacterial strains tested, and therefore the results remain inconclusive for these strains. As with the other

submitted bacterial gene mutation studies, no bacterial strains that test for cross-linking agents were included in the assay, and thus the possibility that this mixture induces cross-linking mutations cannot be ruled out on the basis of the submitted test.

Results of the acute and chronic tests conducted on laboratory animals with Tolcide PS75 technical product and the end-use products, Tolcide PS75LT and Tolcide PS200, are summarized in Appendix I , Tables 2 and 3.

3.2 Determination of Acceptable Daily Intake

An acceptable daily intake is not required, since the proposed uses of tetrakis (hydroxymethyl) phosphonium sulphate do not involve direct food uses.

3.3 Determination of Acute Reference Dose

An acute reference dose is not required, since the proposed uses of tetrakis (hydroxymethyl) phosphonium sulphate do not involve direct food uses.

3.4 Occupational and Bystander Risk Assessment

Occupational exposure to the end use-products, Tolcide PS 75LT and Tolcide PS200, will occur predominantly through the dermal and inhalation routes. This exposure scenario is characterized as intermittent in nature but of a long-term duration. The toxicology database was not considered adequate to completely characterize the potential hazards posed from the use of Tolcide PS75LT and Tolcide PS200.

As the use of Tolcide PS75LT or Tolcide PS200 in evaporative cooling towers and oilfield operations is limited to closed loading and transfer systems in which the occupational exposure (handler and postapplication) is determined to be negligible, toxicological endpoints were not required.

Tolcide PS200 was proposed for use in pulp and paper processing facilities. Workers in the pulp and paper processing facilities may be exposed to mist downstream of the site of application. No data were submitted for the characterization of the level of worker exposure to mist and to tetrakis (hydroxymethyl) phosphonium sulphate and its by-products in pulp and paper facilities. Therefore, a risk assessment for this scenario could not be conducted and the use in pulp and paper processing facilities was not accepted to appear on the Tolcide PS75LT label.

3.4.1 Dermal Absorption

An in vivo dermal absorption study in rats was submitted. An estimate of the dermal absorption was determined based on results obtained from the low dose groups (1.05 mg/cm^2) since percent dermal absorption was the greatest at this level. A dermal absorption value of 10% is recommended based on the highest total absorbed dose found at 24 hours postapplication

(9.13% of the administered dose) and including the maximum amount found in expired air at 96 hours postapplication (0.82%). This value is considered conservative as it includes a significant portion of skin bound residues (5.88%).

3.4.2 Occupational Exposure and Risk

The exposure to handlers is expected to be limited as the end use products are to be used in closed delivery systems in oil field operations and evaporative cooling towers. Exposure may occur during changing of drums or bulk containers, but this activity is very brief and is considered in this assessment to take place once or twice per week throughout the year. Therefore, this exposure duration is considered intermittent, long-term.

3.4.2.1 Mixer, Loader and Applicator Exposure and Risk Assessment

There is potential for exposure to workers mixing/loading and applying Tolcide PS75 LT or Tolcide PS200 solutions. To mitigate exposure to handlers mixing, loading and applying Tolcide PS75LT or Tolcide PS200 solutions, a statement limiting these end use products use to closed loading and transfer systems (i.e. dry coupling) is required to appear on the primary panel of the Tolcide PS75LT and Tolcide PS200 labels. This is expected to result in negligible exposure to occupational handlers mixing, loading and applying Tolcide PS75LT or Tolcide PS200. Therefore, a risk assessment for handlers was not required.

3.4.2.2 Postapplication Worker Exposure and Risk Assessment

Postapplication exposure is likely for the secondary handlers, workers who may be exposed to treated waters at the different facilities, and for the consumer handler, individuals exposed from handling the treated material. Based on information provided by the applicant to characterize postapplication exposures through use description information and two postapplication residue studies, there is a potential for exposure to workers entering areas where water treated with Tolcide PS75LT or Tolcide PS200 products is handled.

3.4.2.2.1 Secondary Worker Exposure

Exposure to tetrakis (hydroxymethyl) phosphonium sulphate and its by-products could occur to workers who may come into contact with treated solutions. Oil field work sites are subject to Occupational Health and Safety legislation, and exposure may be adequately mitigated by existing industrial hygiene practices for petroleum production workers. Potential exposure to drift from treated evaporative cooling tower is considered negligible since there are no anticipated regular worker activities in the area of evaporative cooling towers.

3.4.2.2.2 Bystander Exposure

There is negligible potential for bystander exposure to Tolcide PS75 LT or Tolcide PS200 products, or to tetrakis (hydroxymethyl) phosphonium sulphate and its by-products, due to the industrial nature of the uses of these products.

3.4.3 Handler Exposure and Risk

There are no domestic class products; therefore, a residential handler assessment was not required.

3.5 Food Residues Exposure Assessment

As there are no food or feed uses for tetrakis (hydroxymethyl) phosphonium sulphate, a dietary risk assessment was not conducted.

4.0 Impact on the Environment

4.1 Fate and Behaviour in the Environment

Tetrakis (hydroxymethyl) phosphonium sulphate may reach water systems through the disposal of effluent waters from paper processing and evaporative cooling tower use. The aerobic and anaerobic water/soil biotransformation studies indicate that tetrakis (hydroxymethyl) phosphonium sulphate will be rapidly mineralized to carbon dioxide (CO_2) upon entering the aquatic environment, with the estimated DT_{50} values in the aerobic and anaerobic waters of approximately 6 and 5 days, respectively. Minor amounts of trishydroxymethyl phosphine oxide, trishydroxymethyl phosphine oxide and bishydroxymethyl phosphinic acid were detected in the water layer of the aerobic and anaerobic water/soil biotransformation studies, respectively. Based on the low to moderate adsorption of tetrakis (hydroxymethyl) phosphonium sulfate in the batch equilibrium studies, there would be limited potential for tetrakis (hydroxymethyl) phosphonium sulphate to partition into sediment or organic matter in the aquatic environment. Although the relative amounts of tetrakis (hydroxymethyl) phosphonium sulphate and trishydroxymethyl phosphine oxide are governed principally by pH (tetrakis (hydroxymethyl) phosphonium sulphate hydrolyses under alkaline conditions), hydrolysis is not expected to contribute significantly to the transformation of tetrakis (hydroxymethyl) phosphonium sulphate in surface waters as the rate of mineralization of tetrakis (hydroxymethyl) phosphonium sulphate to CO_2 is faster rate than the rate of hydrolysis of tetrakis (hydroxymethyl) phosphonium sulphate. Phototransformation and volatilization are not expected to be significant routes of transformation of tetrakis (hydroxymethyl) phosphonium sulphate in the environment. Tetrakis (hydroxymethyl) phosphonium sulphate has limited potential to partition into sediment or organic matter and is non-persistent in the aquatic system. Under conditions of actual use in an industrial cooling tower treatment at a starting concentration of 116 mg tetrakis (hydroxymethyl) phosphonium sulphate/L, tetrakis (hydroxymethyl) phosphonium sulphate was below the detection limit (0.5 mg/L) at the point of discharge to the watercourse.

Tetrakis (hydroxymethyl) phosphonium sulphate is not expected to enter the soil during its use as a slimicide in oilfield operations and evaporative cooling towers. Tetrakis (hydroxymethyl) phosphonium sulphate residues are, therefore, not expected to be found in the terrestrial environment.

The vapour pressure and Henry's law constant indicate that tetrakis (hydroxymethyl) phosphonium sulphate is not expected to volatilize in the environment; therefore, tetrakis (hydroxymethyl) phosphonium sulphate residues are not expected in the atmosphere and long-range transport is not expected.

Data on the fate and behaviour of tetrakis (hydroxymethyl) phosphonium sulphate and its major transformation products are summarized in Appendix I, Table 5.

4.2 Effects on Non-Target Species

To estimate risk of potential adverse effects on non-target species, a quotient method is used. The risk quotient is calculated by dividing the exposure estimate by the toxicity endpoint. Low risk is predicted if the risk quotient is less than the trigger value of one. Risk increases with risk quotient values greater than one. If the trigger values are exceeded under the realistic worst-case scenario, then a refinement of the assessment is necessary to evaluate how frequently impacts might be expected in the range of conditions that occur in the field. A refined assessment takes into consideration more realistic exposure scenarios (for example, drift to non-target habitats and runoff to water bodies) and may consider different toxicity endpoints.

4.2.1 Effects on Terrestrial Organisms

For terrestrial vertebrates, tetrakis (hydroxymethyl) phosphonium sulphate caused mortality to birds at a concentration of 227 mg a.i./kg body weight when administered by gavage. Dietary short-term exposure of birds to tetrakis (hydroxymethyl) phosphonium sulphate at a concentration of 650 mg a.i./kg diet caused mortality to birds. No clinical signs of toxicity or treatment-related effects were observed for body weight or feed consumption in any of the surviving birds. The exposure of terrestrial organisms to tetrakis (hydroxymethyl) phosphonium sulphate is not expected to occur due to the use pattern, a risk assessment for terrestrial organisms was, not conducted. See data in Appendix I, Table 7.

4.2.2 Effects on Aquatic Organisms

Risk of tetrakis (hydroxymethyl) phosphonium sulphate to aquatic organisms was based upon evaluation of toxicity data for five freshwater species (one invertebrate, two fish, one alga, and one vascular plant) and three estuarine/marine species (two invertebrate and one fish) (Appendix I,Table 6). Although studies on two aquatic freshwater species (one invertebrate and one fish) were submitted for trishydroxymethyl phosphine oxide, the minor transformation product of tetrakis (hydroxymethyl) phosphonium sulphate, a risk assessment was not conducted, as trishydroxymethyl phosphine oxide residues are not expected to be found in the aquatic environment.

In acute dose-response studies, tetrakis (hydroxymethyl) phosphonium sulphate caused sublethal effects at various concentrations for daphnids, mysid shrimp, all fish species and eastern oyster (NOEC values between 0.72 mg a.i./L and 67.4 mg a.i./L). Tetrakis (hydroxymethyl) phosphonium sulfate was toxic to vascular plants at concentrations greater than 0.625 mg a.i./L. Trishydroxymethyl phosphine oxide did not cause mortality or sublethal effects in acute dose

response study to daphnids and caused only one mortality at the highest concentration tested on fish. Risk quotients calculated under actual use conditions indicate that tetrakis (hydroxymethyl) phosphonium sulphate presents a low risk to daphnids, freshwater and marine fish, eastern oyster and algae following acute exposure; risk quotients are less than one (Appendix I, Table 7).

Deleterious effects (reduced fecundity in the parental generation) were reported following chronic exposure of daphnids to tetrakis (hydroxymethyl) phosphonium sulphate at concentrations higher than 32 µg a.i./L. On an acute basis, tetrakis (hydroxymethyl) phosphonium sulphate negatively affected biomass of the freshwater green alga at concentrations of 63 µg a.i./L. Risk quotients calculated under actual use conditions exceeded the trigger value for these organisms (Appendix I, Table 8). Label statements indicating the toxicity of this pesticide to aquatic organisms and to minimize exposure to the aquatic environment must appear on the product labels.

5.0 Value

5.1 Effectiveness Against Pests

Data from eight laboratory studies were submitted. For each trial an appropriate experimental design was used, which generally consisted of inoculating synthetic process waters with various isolates and monitoring the effect of different concentrations of tetrakis (hydroxymethyl) phosphonium sulphate on the microorganisms. The growth of general heterotrophic bacteria (GHB) was identified by turbidity in the medium, while iron sulphide precipitation was the indicator for sulfate reducing bacteria (SRB). Controls in which no tetrakis (hydroxymethyl) phosphonium sulphate was added to the cultures were used as a reference to determine the degree of biocidal action over time. While this method of bacterial quantification is not as precise as plate counts, it was shown to be reproducible within one log, which was sufficient to discriminate the degree of kill of the 8-log inoculum within the simulated process fluids. No operational trails were submitted. The submitted laboratory trials were sufficient to demonstrate the effectiveness of the products. However, operational trials will be necessary to establish lowest effective rates.

5.1.1 Acceptable Efficacy Claims

5.1.1.1 Tolcide PS75LT and Tolcide PS200 as Oilfield Slimicides

The submitted data from two laboratory studies established effective initial and maintenance dose rates for Tolcide PS75LT and Tolcide PS200 in water flooding operations as summarized in Table 5.1.1.1.1. The use of these products to treat heavily-fouled systems was not supported by sufficient data. Systems with heavy fouling must be cleaned first prior to treatment. Operational trials are required to confirm that the rates and frequencies established from the laboratory data are appropriate for the oilfield use.

Table 5.1.1.1.1 Microbial Slime Control Claims for Tolcide PS75LT and Tolcide PS200 in Oilfield Water flooding Operations

Dosing	Application Rate/L of Process Fluid			Frequency
	mg a.i./L	mg PS75LT/L	mg PS200/L	
Initial	up to 250	up to 330	up to 1250	for 1–3 hours
Maintenance	up to 40	up to 55	up to 200	Continuously

5.1.1.2 Tolcide PS200 as a Slimicide for Evaporative Cooling Towers

The data from laboratory trials using bacterial culture isolated from cooling water samples and to inoculate sterile cooling tower water established effective maintenance doses for Tolcide PS200 as summarized in Table 5.1.1.2.1. The use of this product to treat heavily-fouled systems was not supported by sufficient data. Systems with heavy fouling must be cleaned first prior to treatment. Operational trials are required to confirm that the rates and frequencies established from the laboratory data are appropriate for the evaporative cooling tower use.

Table 5.1.1.2.1 Microbial Slime Control Claims for Tolcide PS200 in Evaporative Cooling Towers

Dosing	Application Rate/L of Process Fluid		Frequency
	mg a.i./L	mg PS200/L	
Maintenance	19–100	95–500	shot dose up to 4 times daily

5.2 Economics

Economic assessment was not conducted.

5.3 Sustainability

5.3.1 Survey of Alternatives

The availability Tolcide PS200 and Tolcide PS75LT provide an additional active ingredient for use in microbial slime control. Thermal and mechanical methods exist for controlling slime formation in industrial process waters, however, these methods tend to be expensive and are not always effective or compatible with the process.

Damaging biofilms are formed by diverse microorganisms under a wide range of different conditions. Furthermore, some biocides may be chemically incompatible with some industrial processes or other chemicals. For this reason, it is important to have a number of different biocides available. There are approximately 300 slimicide products currently registered in Canada for use in evaporative cooling towers and oilfield water injection systems. These are generally broad-spectrum biocides based on a number of different active ingredients with modes of action ranging from oxidizing compounds to membrane-disrupting surfactants.

The key options available for microbial slime control for oilfield operations, paper processing and evaporative cooling tower uses are summarized in Appendix I, Tables 8, 9 and 10.

5.3.2 Compatibility with Current Management Practices Including Integrated Pest Management

Tolcide PS200 and Tolcide PS75LT offers a new broad-spectrum biocide to the range of currently registered slimicide products. They are compatible in general with aqueous industrial process fluids, but may be incompatible with certain additive chemicals used in some specific operations. For instance, the active ingredient tetrakis (hydroxymethyl) phosphonium sulphate is known to be incompatible with 2-mercaptobenzothiazole, a corrosion inhibitor used in some industrial process fluids.

5.3.3 Information on the Occurrence or Possible Occurrence of the Development of Resistance

By their very nature, microbes which form biofilm slimes tend to be more resistant to biocides than the same species of microbe in their free-floating state. Many slimicides, including Tolcide PS200 and Tolcide PS75LT, are intended to kill planktonic microbes in the industrial process fluids, reducing their numbers and preventing biofilms from forming. The active ingredient tetrakis (hydroxymethyl) phosphonium sulphate is a broad-spectrum biocide with a mode of action to disrupt cellular membranes. Long-term resistance to tetrakis (hydroxymethyl) phosphonium sulphate is not expected to develop due to the mode of action and to the industry's current practice of regularly alternating slimicide products.

6.0 Toxic Substances Management Policy Considerations

The management of toxic substances is guided by the federal government's Toxic Substances Management Policy (TSMP), which puts forward a preventive and precautionary approach to deal with substances that enter the environment and could harm the environment or human health. The policy provides decision makers with direction and sets out a science-based management framework to ensure that federal programs are consistent with its objectives. One of the key management objectives is virtual elimination from the environment of toxic substances that result predominantly from human activity and that are persistent and bioaccumulative. These substances are referred to in the policy as Track 1 substances.

During the review process, tetrakis (hydroxymethyl) phosphonium sulphate was assessed in accordance with PMRA Regulatory Directive DIR99-03, *The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy*. Substances associated with the use of tetrakis (hydroxymethyl) phosphonium sulphate were also considered, including major transformation products formed in the environment, microcontaminants in the technical product and formulants in the end-use products, Tolcide PS75LT, and Tolcide PS200. The PMRA has reached the following conclusions:

- Tetrakis (hydroxymethyl) phosphonium sulphate does not meet the criteria for persistence. Its value for half-life in water (approximately 6 days) is below the TSMP Track 1 cut-off criteria for water (>182 days). Tetrakis (hydroxymethyl) phosphonium sulphate is not bioaccumulative; the *n*-octanol–water partition coefficient (log K_{ow}) is less than 0, which is below the TSMP Track 1 cut-off criterion of ≥5.0. As tetrakis (hydroxymethyl) phosphonium sulphate does not meet all Track 1 criteria, it is not classified as a Track 1 substance.

- The technical product Tolcide PS75 contains formaldehyde as a component at a level of 0.085%. Tolcide PS75 does not contain any other contaminants of health or environmental concern identified in the *Canada Gazette*, Part II, Volume 139, Number 24, pages 2641–2643: *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern*.

- The end-use products, Tolcide PS75LT, and Tolcide PS 200, do not contain any formulants of health or environmental concern identified in the *Canada Gazette*, Part II, Volume 139, Number 24, pages 2641–2643: *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern*.

Therefore, the use of tetrakis (hydroxymethyl) phosphonium sulphate is not expected to result in the entry of Track 1 substances into the environment.

7.0 Summary

7.1 Human Health and Safety

Mixers, loaders, and applicators handling Tolcide PS75LT and Tolcide PS200 and workers re-entering treated areas on oil field operations and evaporative cooling towers are not expected to be exposed to levels of tetrakis (hydroxymethyl) phosphonium sulphate and its by-products that will result in unacceptable risk when these products are used according to label directions.

A health assessment has been conducted for Tolcide PS75LT and Tolcide PS200. The use of these products in oilfield operations and evaporative cooling towers are not expected to result in an unacceptable risk.

The use of Tolcide PS200 in pulp and paper processing facilities was not adequately characterized and, therefore, this use is not supported on the Tolcide PS200 label. There remain uncertainties/concerns with respect to the toxicology database for this active ingredient.

7.2 Environmental Risk

Tetrakis (hydroxymethyl) phosphonium sulphate presents a low risk to fish, aquatic plants and aquatic invertebrates; however, given that tetrakis (hydroxymethyl) phosphonium sulphate is a slimicide, it is expected to adversely affect alga. Therefore, specific instructions on its toxicity to aquatic organisms and measures to minimize exposure to the aquatic environment must appear on the product label.

7.3 Value

The data submitted to register Tolcide PS200 and PS75LT are adequate to demonstrate efficacy for use in oilfield water floods and evaporating cooling towers. Tolcide PS200 and PS75LT offer a novel slimicide chemistry to the range of currently registered products. This will provide the users with a completely new alternative in industries where it is common practice to alternate slimicide products regularly.

7.4 Unsupported Uses

The proposed use of Tolcide PS200 in pulp and paper processing facilities may result in postapplication exposure. As well the use of Tolcide PS200 in pulp and paper processing facilities was not adequately characterized and, therefore, this use is not supported on the Tolcide PS200 label.

8.0 Regulatory Decision

Health Canada's PMRA, under the authority of the *Pest Control Products Act* and Regulations, has granted conditional registration for the sale and use of the technical product Tolcide PS75 (containing the active ingredient tetrakis (hydroxymethyl) phosphonium sulfate) and the end-use products Tolcide PS200 and Tolcide PS75LT to control slime buildup in oilfield flooding and evaporative cooling towers.

An evaluation of available scientific information found that, under approved conditions of use, the product has value and does not present an unacceptable risk to human health or the environment.

Although the risks and value have been found acceptable when all risk-reduction measures are followed, as a condition of these registrations, the following additional scientific information is required from the applicant. For more details, refer to Section 12 Notice associated with these conditional registrations.

Chemistry

The following studies are required to complete the chemistry database for this product:

- Oxidizing and reducing properties of Tolcide PS75LT.

- Storage stability data of Tolcide PS200 stored at ambient temperature for one year.

Environment

- Representative chromatograms of unfortified and fortified surface and drinking water samples generated from the analysis of tetrakis (hydroxymethyl) phosphonium sulphate as well data demonstrating linearity of the ion chromatographic method used to determine tetrakis (hydroxymethyl) phosphonium sulphate in drinking and surface water are required for the residue methods. This study should be submitted within one year of the granting of this conditional registration.

- Develop and validate analytical methodology for tetrakis (hydroxymethyl) phosphonium sulphate and its transformation products using aquatic plant and animal tissues (preferably fish or bird tissue, but mammal tissues are also acceptable). The studies should be conducted using non-labelled tetrakis (hydroxymethyl) phosphonium sulphate and transformation products. Tissue samples should be spiked with the non-labelled compounds, extracted and subsequently analysed. Validation data should include precision, accuracy, recovery, LOQ and linear range. These studies should be submitted within one year of the granting of this conditional registration.

Value

The following studies are required to ensure that the lowest effective rates are being used:

- Operational trials are needed to determine the appropriate frequency of application in the oilfield water flooding and evaporative recirculating cooling tower uses. (Studies to be completed and submitted within one year of the conditional registration being granted).

NOTE: Then PMRA will publish a consultation document at the time there is a proposed decision on applications to convert these conditional registrations to full registrations or on applications to renew the conditional registrations, whichever occurs first.

List of Abbreviations

µg	micrograms
a.i.	active ingredient
atm	atmosphere
bw	body weight
CAS	Chemical Abstracts Service
cm	centimetres
CO_2	carbon dioxide
DNA	deoxyribonucleic acid
DT_{50}	dissipation time 50% (the dose required to observe a 50% decline in the test population)
EC_{25}	effective concentration on 25% of the population
g	gram
Hg	mercury
IUPAC	International Union of Pure and Applied Chemistry
kg	kilogram
K_d	soil-water partition coefficient
K_{oc}	organic-carbon partition coefficient
K_{ow}	*n*-octanol–water partition coefficient
L	litre
LC_{50}	lethal concentration 50%
LD_{50}	lethal dose 50%
LOAEL	lowest observed adverse effect level
LOQ	limit of quantitation
mg	milligram
mL	millilitre
MAS	maximum average score
N/A	not applicable
NTP	National Toxicology Program
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
OC	organic carbon content
p*K*a	dissociation constant
PMRA	Pest Management Regulatory Agency
ppb	parts per billion
RSD	relative standard deviation
SRB	sulfate reducing bacteria
$t_{1/2}$	half-life
THPO	trishydroxymethyl phosphine oxide
THPS	tetrakis (hydroxymethyl) phosphonium sulphate
TSMP	Toxic Substances Management Policy
v/v	volume per volume dilution

Appendix I Tables and Figures

Table 1 Residue Analysis

Matrix	Analyte	Method Type	LOQ	Reference
Plant	To be submitted as a condition of registration			
Animal	To be submitted as a condition of registration			
Soil	Waiver request based on the fact that parent and degradates do not adsorb to soil and sediment. Waiver accepted.			783416
Sediment	Waiver request based on the fact that parent and degradates do not adsorb to soil and sediment. Waiver accepted.			783416
Water	THPS	Ion Chromatography	25 ppb in surface water 25 ppb in drinking water	908703

Table 2 Acute Toxicity of Tolcide PS75 (tetrakis [hydroxymethyl] phosphonium sulphate)

Study Type	Species	Result	Comment	Reference
Acute Toxicity of Tolcide PS75				
Oral	Rat (HC/CFY remote Sprague-Dawley)	LD_{50} (M) = 622 mg/kg bw LD_{50} (F) = 518 mg/kg bw LD_{50} (M/F) = 575 mg/kg bw	**MODERATE** Toxicity	783376
Oral	Rat (Sprague-Dawley)	LD_{50} (M) = 333 mg/kg bw LD_{50} (F) = 253 mg/kg bw LD_{50} (M/F) = 289 mg/kg bw	**HIGH** Toxicity	783375
Oral	Rat (F344/N)	LD_{50} (M) = 333 mg/kg bw LD_{50} (F) = 248 mg/kg bw	**HIGH** Toxicity	783387 783390
Oral	Mouse ($B6C3F_1$)	200 mg/kg a.i. bw > LD_{50} > 400 mg/kg a.i.bw	**HIGH** Toxicity	783387 783390
Dermal	Rat (CD Sprague-Dawley)	LD_{50} > 2000 mg/kg bw	**LOW** Toxicity	783377 908712
Inhalation	Rat (Sprague-Dawley IGS)	LC_{50} (M) = 0.628 mg/L LC_{50} (F) = 0.551 mg/L LC_{50} (M/F) = 0.591 mg/L	**SLIGHT** Toxicity	1440849
Inhalation	Rat (Sprague-Dawley)	LC_{50} = 5.55 mg/L	**Study unacceptable** due to problems with achieved particle size (MMAD > 4.0 µm).	783378 908713
Skin irritation	Rabbit (New Zealand White)	MAS[a] = 0.0	**Non-irritating**	783379 908715

Study Type	Species	Result	Comment	Reference
Eye irritation	Rabbit (New Zealand White)	Corneal opacity and necrosis of eyelids noted at 24 hours	**Extremely irritating**	783380 908714
Skin sensitization (maximization)	Guinea pig	Positive	**Potential Dermal Sensitizer**	783381 908716

[a] MAS = maximum average score for 24, 48 and 72 hours

Table 3 Toxicity Profile of Tolcide PS75 (Tetrakis [hydroxymethyl] phosphonium sulphate)

Study Type	Species	Results[a,b] (mg/kg bw/day)	Reference
14-day oral	Rat (F344/N)	A NOAEL and LOAEL were not established as this study was considered supplemental (range-finding study). No effects were noted at 12.5 mg/kg bw/day. Effects noted at the next highest dose (25 mg/kg bw/day) included decreased body weight and body weight gain.	783387 783390
28-day oral gavage (Range-finding)	Rat (Sprague-Dawley)	A NOAEL and LOAEL were not established as this study was considered supplemental (range-finding study). No effects were noted at 4.5 mg/kg bw/day. Effects noted at the next highest dose (22.7 mg/kg bw/day) included clinical signs of toxicity, decreased body weight and body weight gain, and changes in liver and kidney weights.	783383
90-day oral gavage Neurological assessment (vision, audition and pain perception, footspread and gripstrength measurements) conducted on control and high dose animals.	Rat (Sprague-Dawley)	**NOAEL**: 0.76 mg/kg bw/day **LOAEL**: 3.8 mg/kg bw/day; vacuolation of periportal hepatocytes (♂)	783382 908717
90-day oral gavage	Rat (F344/N)	A NOAEL and LOAEL were not established as this study was considered supplemental (range-finding study). Effects were noted at the lowest dose tested (5 mg/kg bw/day), which included decreased body weight and body weight gain (♀), and diarrhea.	783387 783389 783390

Study Type	Species	Results[a,b] (mg/kg bw/day)	Reference
28-day dermal (Range-finding)	Rat (Sprague-Dawley)	A NOAEL and LOAEL were not established as this study was considered supplemental (range-finding study). Effects were noted at the lowest dose tested (19 mg/kg bw/day) which included erythema and edema (♂/♀), as well as decreased body weight gain and food consumption (♂).	783385 908732
14-day oral	Mouse ($B6C3F_1$)	A NOAEL and LOAEL were not established as this study was considered supplemental (range-finding study). Decreased body weight gain was noted in females at the lowest dose tested (12.5 mg/kg bw/day). No effects were noted for males at the lowest dose tested. Effects noted for males at the next highest dose (25 mg/kg bw/day) included decreased body weight and body weight gain.	783387 783390
90-day oral gavage	Mouse ($B6C3F_1$)	A NOAEL and LOAEL were not established as this study was considered supplemental (range-finding study). No effects were noted at the lowest dose tested (10 mg/kg bw/day). Effects noted at the next highest dose (20 mg/kg bw/day) included decreased body weight and body weight gain (♂/♀), as well as periportal vacuolar degeneration (♂).	783387 783390
Carcinogenicity (24 month gavage)	Rat (F344/N)	A **NOAEL** and **LOAEL** were not established due to study limitations. Effects were noted at 5 mg/kg bw/day, including rough hair coat, diarrhea, decreased survival (♂), and cystic degeneration in the liver (♂). Evidence of carcinogenicity based on increased incidence of endometrial stromal polyps (♀) at 10 mg/kg bw/day.	783387 783390 908734 910816 910822
Carcinogenicity (24-month gavage)	Mouse ($B6C3F_1$)	A **NOAEL** and **LOAEL** were not established due to study limitations. Effects were noted at 5 mg/kg bw/day,including; rough hair coat, diarrhea, focal hyperplasia of the adrenal capsule, granulocytic hyperplasia of the bone marrow (♀), dilatation of the uterus (♀), hematopoiesis of the liver (♂), lymphoid depletion of the thymus (♂), focal atrophy of the spermatogenic epithelium (♂), lung congestion (♂), focal hyperplasia of the adrenal medulla (♂). Evidence of carcinogenicity based on increased incidences of endometrial stromal polyps (♀), and pheochromocytomas (♂) at 10 mg/kg bw/day.	783387 783390 908734 910816 910822 1221555

Study Type	Species	Results[a,b] (mg/kg bw/day)	Reference
Two-generation reproduction	Rat (Sprague-Dawley IGS)	**Parental systemic NOAEL**: 0.78 mg/kg bw/day **Parental systemic LOAEL**: 5.9 mg/kg bw/day; decreased body weight and bodyweight gain, increased uterine and adrenal weight (♂), and liver pathology (periportal hepatocyte enlargement [♂] and/or vacuolation) in the first generation; liver pathology (periportal hepatocyte enlargement and vacuolation, bile duct proliferation [♂], and focal hepatocyte necrosis [♂]) and increased adrenal weight (♂) in the second generation. Reproductive and offspring NOAELs and LOAELs could not be established due to uncertainties with the study, which included a high incidence of offspring deaths in the control groups, and conflicting information presented in the study report. There was an indication of increased pup deaths (prior to postnatal day 1) at the high dose in the first generation, and at all dose levels in the 2nd generation. **Study unacceptable.**	783391 783392 908724 908725 910818 910820 1286994 1286995 1288017 1288018 1288019 1288352 1288353 1288354 1288355 1288356 1288357 1288358 1288359 1288360 1288361 1288362 1288363 1306378 1410697
Developmental toxicity	Rat (Sprague-Dawley)	A NOAEL and LOAEL were not established as this study was considered supplemental (range-finding study). No effects were noted in maternal animals at the lowest dose tested (23 mg/kg bw/day). Maternal effects noted at the next highest dose (45 mg/kg bw/day) included decreased bodyweight gain (↓20% over GD 3-20) and food consumption. No fetal effects were noted at the lowest dose tested (23 mg/kg bw/day). Fetal effects noted at the next highest dose (45 mg/kg bw/day) included decreased body weight (↓8%).	783393 908727
Developmental toxicity	Rat (Sprague-Dawley)	**Maternal NOAEL**: 11 mg/kg bw/day **Maternal LOAEL**: 23 mg/kg bw/day; salivation and/or red/brown staining, increased incidence and severity of gastrointestinal lesions (thickening of mucosal surface of stomach or duodenum), and increased incidence of liver mottling and paleness. **Developmental NOAEL**: 23 mg/kg bw/day **Developmental LOAEL**: 45 mg/kg bw/day; eye malformations (one fetus with anophthalmia and a small eye socket, and another, from a separate litter, with a hemorrhagic eye) and increased number of fetuses (and litters) with extra thoraco-lumbar ribs.	783394 908726

Study Type	Species	Results[a,b] (mg/kg bw/day)	Reference
Developmental toxicity	Rabbit (NZW)	A NOAEL and LOAEL were not established as this study was considered supplemental (range-finding study). Effects were noted in maternal animals at the lowest dose tested (30 mg/kg bw/day), including decreased body weight gain and food consumption during the dosing period. No fetal effects were noted at the highest dose tested (60 mg/kg bw/day).	783395 908729
Developmental toxicity	Rabbit (NZW)	**Maternal NOAEL**: 13.5 mg/kg bw/day **Maternal LOAEL**: 45 mg/kg bw/day; decreased body weight gain (↓58%) and food consumption (↓52%) during treatment and over the entire study period, and body weight loss during GD 7-12. **Developmental NOAEL**: 13.5 mg/kg bw/day **Developmental LOAEL**: 45 mg/kg bw/day; increased incidence in external/visceral malformations, eye malformations (42 fetuses with microphthalmia, aphakia, retinal dysplasia, or iris malformed); limb malformations (14 fetuses, involving increased/decreased number of digits and/or fusion of digits), and cardiac malformations (2 fetuses; common carotid hypoplastic, marked dilatation of aortic arch). Increased incidence of skeletal malformations; malformations primarily of the skull (incl. eye socket↓in size, parietal malformed) and limbs (absent/malformed or malpositioned bones). Increased incidence of skeletal variations (primarily extra thoraco-lumbar ribs).	783396 908728
Gene mutations in bacteria	*Salmonella typhimurium*	**Negative** for strains TA 98, TA100, TA 1535, TA 1537 and TA 1538. Note: No strains were used to detect cross-linking agents.	783397 908730
Gene mutations in mammalian cells in vitro	Mouse lymphoma L5178Y cells (TK locus)	**Positive** Colony size distributions were predominantly smaller relative to the negative control, indicating that THPS may induce gross chromosomal aberrations rather than point mutations. However, there was limited confidence in these results due to study limitations (one or two treatment groups per experiment, no criteria defining colony sizes).	783400 783401 908692
Unscheduled DNA synthesis (in vitro)	Primary rat hepatocytes (male F344 rat)	**Negative** **Unacceptable** due to study deficiencies. Insufficient sample size (1 rat) and inadequate positive controls.	783398 783399 908731

Study Type	Species	Results[a,b] (mg/kg bw/day)	Reference
Mammalian chromosomal aberration (in vitro)	Chinese hamster ovary cells	**Positive** In presence and absence of activation (Note: Enhanced response in presence of S9 activation)	783402 908693
Micronucleus assay (in vivo)	Mice (Male CD-1 [ICR])	**Negative** **375 mg/kg bw**: mortality at 24 or 48 hours (2/7 males per timepoint). Clinical signs in those that prematurely died: hunched posture, decreased respiratory rate, laboured respiration, dehydration, tip-toe gait, lethargy, piloerection, ataxia, pallor of the extremities, splayed gait, and ptosis. Hunched posture also observed in 2/7 males that did not die prematurely in the 24 hr sampling group.	783405 908695
Dominant Lethal in rat (in vivo)	Rat (Male Sprague-Dawley)	**Equivocal** There were statistically significant increases in post-implantation losses in week 2 but not in week 1. **Supplementary** due to non-standard dosing regime.	783403 783404 908694
Metabolism	Rat (Sprague-Dawley)	**Absorption** Rapidly absorbed in blood and plasma (T_{max} 0.5–2 h). Peak concentration was higher in plasma than blood. Absorption decreased at the high dose (based on an approximately 30-fold higher $AUC_{(0-\infty)}$ in high dose vs low dose animals , which was lower than the 50-fold increase in dose-level) indicating saturation. Total absorption estimates ranged from 30-34% in males and females following 7 days, and from 48-64% following 48 hours when expired air was included. **Distribution** Pharmacokinetics were similar between the sexes at the low dose, but at the high dose males demonstrated a greater distribution and slower elimination in blood, with the reverse in plasma. Tissue/organ distribution was not assessed in the submitted studies. **Excretion** The rate of elimination was slower in blood than plasma ($T_{1/2}$ was 59–74 h in plasma, 126–195h in blood). Primary excretion routes were urine and feces. A minor amount remained in the carcass, and a minimal amount in cage wash and cage debris. Excretion patterns were similar between sexes but males excreted slightly more in faeces while females excreted slightly more in urine. Expiration in air was measured up to 13% over 2 days, but was postulated to account for up to 30% when unaccounted mass balance was taken into consideration.	783410 783411 908700

Study Type	Species	Results[a,b] (mg/kg bw/day)	Reference
		Metabolism No parent compound was detected in urine, and 9 metabolites were detected. The primary metabolite was trishydroxymethyl phosphine oxide (**THPO**; accounting for ≤10% of the administered dose). None of the other 8 metabolites (each accounting for ≤4%) were positively identified, but two were postulated to be 2-hydroxyethylphosphonic acid (**BHMPA**) and a formaldehyde adduct of THPO. No parent compound was detected in faeces, and 7 metabolites were detected (common to those detected in urine). The primary metabolite in faeces was THPO (accounting for 14-24%); the others each accounted for ≤7%.	

[a] Effects observed in males as well as females unless otherwise reported
[b] Doses corrected for THPS content, unless otherwise specified.

Table 4 Toxicity studies conducted with trihydroxymethyl phosphine oxide (THPO; a major metabolite of tetrakis [hydroxymethyl] phosphonium sulphate)

Study Type	Species	Results[a] (mg/kg bw/day)	Reference
Oral	Rat (CD Sprague-Dawley)	**LD_{50}> 2000 mg/kg bw** **LOW** Toxicity	783412 908701 908710
28-day dermal	Rat (Sprague-Dawley)	**NOAEL (dermal irritation)**: not established since effects were noted at the lowest dose tested. **LOAEL (dermal irritation)**: 300 mg/kg bw/day; dermal irritation (macroscopic and histopathological), increasing in incidence and/or severity with increased dose (♂ more severely affected). **NOAEL (systemic toxicity)**: 650 mg/kg bw/day **LOAEL (systemic toxicity)**: 1000 mg/kg bw/day; increased neutrophil count (♀) and total protein (♀), decreased A/G (♀), and adrenal cortical hypertrophy in both sexes.	783413 908709
Gene mutations in bacteria	*Salmonella typhimurium*	**Negative** Acceptable for TA 98. **Unacceptable** for TA 100, TA 1535, TA 1537, and *E. coli* WP2uvrA due to absence of, or inadequate, positive controls. Note: No strains were used to detect cross-linking agents.	783408 908697
Gene mutations in mammalian cells (in vitro)	Mouse lymphoma L5178Y cells (TK locus)	**Negative**	783409 908698
Chromosome aberrations (in vitro)	Chinese hamster ovary cells	**Negative** **Supplementary** due to inadequate dosing.	783407 908696

Table 5 Fate and Behaviour in the Environment

Study Type	Test Substance	Study Conditions	Value	Major Transformation Products*	Reference (PMRA)
Soil					
Adsorption/desorption	THPS	Agricultural sand:# $K_{d\text{-}ads}$ $K_{oc\text{-}ads}$	0.27156156	N/A	783426
		Silt loam: $K_{d\text{-}ads}$ $K_{oc\text{-}ads}$	0.363232	N/A	
		Pond sediment: $K_{d\text{-}ads}$ $K_{oc\text{-}ads}$	0.8499	N/A	
		Sandy loam: $K_{d\text{-}ads}$ $K_{oc\text{-}ads}$	0.344949	N/A	
		Marine sediment: $K_{d\text{-}ads}$ $K_{oc\text{-}ads}$	0.198383	N/A	
		Sandy loam nonautoclaved: $K_{d\text{-}ads}$ $K_{oc\text{-}ads}$	0.71101101	N/A	
		Sandy loam autoclaved: $K_{d\text{-}ads}$ $K_{oc\text{-}ads}$	0.466666	N/A	
Aquatic systems					
Hydrolysis	THPS	25°C at: pH 5 pH7 pH9	 $t_{½}$ = 133 d $t_{½}$ = 72.2 d $t_{½}$ = 6.83 d	 THPO (17.8%; day 29) THPO (28%; day 29) THPO(95.9%;day 28)	783420
Phototransformation	THPS	25°C at: pH 5 pH 7	 $t_{1/2}$ dark = 3.78 d $t_{1/2}$ irradiated = 3.87 d t1/2 dark = 8.46 d t1/2 irradiated = 7.37 d	 THPO (46.3–60.6%)	908708
Aerobic metabolism	THPS	25°C Well water pH 6.4–7.79 Sandy loamy soil %OC 1.2%	Water: DT_{50}: approx. 6 d Whole system: DT_{50}: less than 7 days	CO_2 (69.6%; day 21)	783423
Anaerobic metabolism	THPS	25°C Well water pH 5.44–6.22 Sandy loam soil %OC 1.2%	Water: DT_{50}: less than 5 d Whole system: DT_{50}: less than 7 days	CO_2 (80.3%; day 365)	783424

*Numbers in parentheses represent maximum concentrations [as % of applied] and time [days] to maximum concentration.
K_{oc}: non-Freundlich adsorption coefficient; K_d: soil-water partition coefficient.

Table 6 Toxicity to Non-Target Species

Organism	Species	Study Type	Test Substance	Toxicity Data	Reference (PMRA #)
Terrestrial Organisms					
Birds	Bobwhite quail	Short-term dietary	THPS	NOEC: 325 mg a.i./kg diet (mortality) LC_{50}: 2414 mg a.i./kg diet	783453
	Mallard duck	Acute oral	THPS	NOEC: 126 mg a.i./kg bw LD_{50}: 311 mg a.i./kg bw	783452
		Short-term dietary	THPS	NOEC: 570 mg a.i./kg diet (mortality) LC_{50}: between 1083 and 2058 mg a.i./kg diet	783454
Freshwater Organisms					
Invertebrates	*Daphnia magna*	Acute	THPS	EC_{50}: 19.4 mg a.i./L NOEC: 10.4 mg a.i./L (immobilization)	783431
			THPO	EC_{50}: > 1000 mg a.i./L NOEC: ≥ 1000 mg a.i./L (immobilization)	783432
		Chronic	THPS	NOEC: 32 µg a.i./L (reproduction)	783433
Fish	Rainbow trout	Acute	THPS	LC_{50}: between 65.8 and 110 mg a.i./L NOEC: 13.6 mg a.i./L	783445
			THPO	LC_{50}: > 5000 mg a.i./L NOEC: 2500 mg a.i./L	783446
	Bluegill sunfish	Acute	THPS	LC_{50}: between 67.4 and 208 mg a.i./L NOEC: 67.4 mg a.i./L	783447
Algae	Green alga	*S. capriconutum* 96-h	THPS	EC_{50}: 204 µg a.i./L NOEC: 63 µg a.i./L (biomass)	783456
Plant	*Lemna minor*	Test substance added into the culture medium; 7-d exposure	THPS	EC_{50}: 4.0 mg a.i./L NOEC: 0.625 mg a.i./L (growth/growth rate)	783473

Organism	Species	Study Type	Test Substance	Toxicity Data	Reference (PMRA #)
Estuarine/Marine Organisms					
Invertebrates	Mysid shrimp	Acute	THPS	LC_{50}: 7.4 mg a.i./L NOEC: 7.5 mg a.i./L	783435
	Eastern oyster	Acute	THPS	EC_{50}: 1.6 mg a.i./L NOEC: 0.72 mg a.i./L	783443
Fish	Sheepshead minnow	Acute	THPS	LC_{50}: between 60 and 100 mg a.i./L NOEC: 36 mg a.i./L	783450

Table 7 Screening Level Risk Assessment on Non-Target Species

Organism	Study Type	Test Substance	Toxicity	Exposure[a]	Units	RQ[b]
Freshwater Organisms						
Invertebrates	Acute *Daphnia magna*	THPS	10.4	0.5	mg a.i./L	0.48
	Chronic *Daphnia magna*	THPS	0.032	0.5	mg a.i./L	15.6
Fish	Acute Rainbow trout	THPS	13.6	0.5	mg a.i./L	0.04
	Acute Bluegill sunfish	THPS	67.4	0.5	mg a.i./L	0.01
Algae	Acute (96-h)	THPS	0.063	0.5	mg a.i./L	7.94
Plant	Dissolved; 7-d exposure	THPS	0.625	0.5	mg a.i./L	0.8
Estuarine/Marine Organisms—exposure to water body of 30-cm depth directly oversprayed						
Invertebrates	Acute Mysid shrimp	THPS	2.3	0.5	mg a.i./L	0.22
	Mollusk shell deposition	THPS	0.72	0.5	mg a.i./L	0.69
Fish	Acute Sheepshead minnow	THPS	36	0.5	mg a.i./L	0.01

[a] Exposure is based on the use of Tolcide PS75 in an industrial cooling tower treatment facility under actual use conditions (PMRA 783458).
[b] Risk quotient = exposure / toxicity

Table 8 Alternative Slimicides for Oilfield Operations Uses

Active	Example of End-Use Product	Claims	Mode of Action
NABAM; SODIUM DIMETHYLDITHIOCARBAMATE	Aquatreat DNM-30	*Bacillus cereus*; *Desulfovibrio desulfuricans*; *Pseudomonas* sp.; *Aspergillus* sp.; *Penicillium* sp.; *Trichoderma* sp.	unknown
POTASSIUM DIMETHYLDITHIOCARBAMATE	Busan 85	bacteria	unknown
1-ALKYL (C8-C18) -1,3-PROPANEDIAMINE ACETATE	Armohib-654 (etc)	algae, slime-forming bacteria; sulfate-reducing bacteria	unknown
2,2-DIBROMO-3-NITRILOPROPIONAMIDE	Bio-Clear 1000	slime-forming bacteria; sulfate-reducing bacteria	cellular oxidation
ACROLEIN	Magnacide B	bacteria; fungi	unknown
DIDECYL DIMETHYL AMMONIUM CHLORIDE	Magnicide 785	slime-forming bacteria; sulfate-reducing bacteria (*Desulfovibrio desulfuricans*)	membrane disruption
1-ALKYL (C6-C18) 1,3-PROPANE DIAMINE	Aquagaurd 6905	algae, slime-forming bacteria; sulfate-reducing bacteria	unknown

Table 9 Alternative Slimicides for Paper Processing Water Uses

Active	Example of End-Use Product	Claims	Mode of Action
1,2-DIBROMO-2,4-DICYANOBUTANE	Tektamer 2200	bacteria; fungi; yeasts	cellular oxidation
1-BROMO-3-CHLORO-5,5-DIMETHYLHYDANTOIN 1,3-DICHLORO-5,5-DIMETHYLHYDANTOIN 1,3-DICHLORO-5-ETHYL-5 METHYLHYDANTOIN	B.I.O. Blast 650	microbial slimes	cellular oxidation
1-ALKYL (C8-C18)-1,3-PROPANEDIAMINE ACETATE	Rasio 936	bacterial & fungal slimes	unknown
1-BROMO-3-CHLORO-5,5-DIMETHYLHYDANTOIN	Aquate	slime-forming bacteria; fungi; algae	cellular oxidation
2,2-DIBROMO-3-NITRILOPROPIONAMIDE	Fennosan 150-C	bacteria; fungi; yeast	cellular oxidation
2-METHYL-4-ISOTHIAZOLIN-3-ONE 5-CHLORO-2-METHYL-4-ISOTHIAZOLIN-3-ONE	Irgacide PT 286X	slime-forming bacteria; fungi	inhibition of membrane-bound enzymes
BRONOPOL	Rasio 937	slimicide	cellular oxidation

Active	Example of End-Use Product	Claims	Mode of Action
DAZOMET	Amerstat 223	slime-forming bacteria; fungi	unknown
DECYL ISONONYL DIMETHYL AMMONIUM CHLORIDE	Bardac CW-50	bacteria; fungi; algae	membrane disruption
GLUTARALDEHYDE N-ALKYL (40% C12, 50% C14, 10% C16) DIMETHYL BENZYL AMMONIUM CHLORIDE	Nalcon 7637	slime-forming bacteria; sulfate-reducing bacteria; fungi; yeast	protein cross-linking; membrane disruption
GLUTARALDEHYDE	Prior 285	slime-forming bacteria; sulfate-reducing bacteria; fungi; yeast	protein cross-linking
METHYLENE BIS(THIOCYANATE)	Process B-2008	slime-forming and spoilage bacteria	protein alteration
NABAM; SODIUM DIMETHYLDITHIOCARBAMATE	X-Cell 419	papermill slimes	unknown
N-ALKYL (40% C12, 50% C14, 10% C16) DIMETHYL BENZYL AMMONIUM CHLORIDE	Process B-1001	slime-forming bacteria	membrane disruption
SODIUM BROMIDE (+ HYDROCHLORIC ACID)	Basabrom 40	slime-forming bacteria; fungi; algae	cellular oxidation

Table 10 Alternative Slimicides for Evaporative Cooling Tower Uses

Active	Example of End-Use Product	Claims	Mode of Action
1-BROMO-3-CHLORO-5,5-DIMETHYLHYDANTOIN 1,3-DICHLORO-5,5-DIMETHYLHYDANTOIN 1,3-DICHLORO-5-ETHYL-5 METHYLHYDANTOIN	OXIPRO	slime-forming bacteria; fungi; algae	cellular oxidation
1-ALKYL (C8-C18)-1,3-PROPANEDIAMINE ACETATE	CSW 850	bacterial & fungal slimes	Unknown
2,2-DIBROMO-3-NITRILOPROPIONAMIDE	DOW antimicrobial 7287	bacteria; algae	cellular oxidation
2-METHYL-4-ISOTHIAZOLIN-3-ONE 5-CHLORO-2-METHYL-4-ISOTHIAZOLIN-3-ONE	Kathon CF 1400	slime-forming bacteria; fungi	Inhibition of membrane-bound enzymes
BRONOPOL	Aquaguard 62K7	microbial slimes	cellular oxidation
CALCIUM HYPOCHLORITE	Accu Tab	microbial slimes, algae	cellular oxidation
DAZOMET	Spectrum RX 3500	slime-forming bacteria; fungi	Unknown

Active	Example of End-Use Product	Claims	Mode of Action
DECYL ISONONYL DIMETHYL AMMONIUM CHLORIDE	Bardac CW-50	bacteria; fungi; algae	membrane disruption
DIDECYL DIMETHYL AMMONIUM CHLORIDE	Alpha 133	slime-forming bacteria; algae	membrane disruption
DIDECYL DIMETHYL AMMONIUM CHLORIDE DIOCTYL DIMETHYL AMMONIUM CHLORIDE N-ALKYL (40% C12, 50% C14, 10% C16) DIMETHYL BENZYL AMMONIUM CHLORIDE	Econo-cide B 1001	slime-forming bacteria; algae	membrane disruption
DISODIUM CYANODITHIOIMIDOCARBONATE POTASSIUM N-METHYLDITHIOCARBAMATE	Wetcide 4312 Liquid Microbicide	slime-forming bacteria; algae	Unknown
GLUTARALDEHYDE	Myacide GA 50	slime-forming bacteria; sulfate-reducing bacteria; fungi; yeast	protein cross-linking
METHYLENE BIS(THIOCYANATE)	B.I.O. Blast 610	slime-forming and spoilage bacteria	protein alteration
NABAM; SODIUM DIMETHYLDITHIOCARBAMATE	Aquatreat DMN-30	cooling tower slimes	metal chelation
N-ALKYL (40% C12, 50% C14, 10% C16) DIMETHYL BENZYL AMMONIUM CHLORIDE	CSW 825	slime-forming bacteria	membrane disruption
POLY[OXYETHYLENE(DIMETHYLIMINIO)ETHYLENE(DIMETHYLIMINIO)ETHYLENE DICHLORIDE]	Bioquat 20 Liquid Biocide		membrane disruption
POTASSIUM DIMETHYLDITHIOCARBAMATE	Specialty CSW 836 Cooling Tower Biocide	cooling water slimes	Unknown
SODIUM DICHLORO-S-TRIAZINETRIONE	Deep Crystal	Halobriq NDC	cellular oxidation
SODIUM HYPOCHLORITE	Actichlor	bacteria; algae; fungi	cellular oxidation

References

A. List of Studies/Information Submitted by Registrant

1.0 Chemistry

PMRA Document Number: 783359
Reference: 1989, Tetrakis (Hydroxymethyl) Phosphonium Sulfate (THPS): Discussion Of The Formation Of Impurities, TD-11, Data Numbering Code: 2.11.4 Confidential Business Information

PMRA Document Number: 783366
Reference: 1991, Tetrakis (Hydroxymethyl) Phosphonium Sulfate (THPS): Determination Of Physico- Chemical Properties, LSR 91/0304, MRID: 42236303, Data Numbering Code: 2.14.1,2.14.10,2.14.13,2.14.2,2.14.3,2.14.4,2.14.6,2.14.7,2.14.9 Confidential Business Information

PMRA Document Number: 783365
Reference: 1991, Tetrakis (Hydroxymethyl) Phosphonium Sulfate (THPS-75): Determination Of Physico-chemical Properties, LSR 91/0325, MRID: 42236304, Data Numbering Code: 2.14.1,2.14.12,2.14.13,2.14.2,2.14.3,2.14.5,2.14.6 Confidential Business Information

PMRA Document Number: 783373
Reference: 1993, Discussion Of The Flammability, Explodability, And Miscibility Of THPS 75%, AWL-THPS-001, MRID: 42765302, Data Numbering Code: 2.16 Confidential Business Information

PMRA Document Number: 783372
Reference: 1993, THPS 75% : Viscosity Case MRID 42640402, 00404-001, MRID: 42640402, Data Numbering Code: 2.16 Confidential Business Information

PMRA Document Number: 783371
Reference: 1993, THPS 75%: Oxidizing Or Reducing Action Case, 00431-001, MRID: 42765301, Data Numbering Code: 2.16 Confidential Business Information

PMRA Document Number: 783370
Reference: 1994, An Assessment Of The Storage Stability And Corrosion Characteristics Of THPS 75, Ell/747, MRID: 42640401, Data Numbering Code: 2.14.14 Confidential Business Information

PMRA Document Number: 783369
Reference: 1994, Tolcide PS75 : Partition Coefficient N- Octanol/water (HPLC), 60090.aw\tm.001\bioakk, Data Numbering Code: 2.14.11 Confidential Business Information

PMRA Document Number: 783368
Reference: 1995, Physical And Chemical Characteristics Of Tolcide PS75: Vapor Pressure, 120-19, Data Numbering Code: 2.14.9 Confidential Business Information

PMRA Document Number: 783417
Reference: 1996, Analytical Methods For TetrakisHydroxymethyl Phosphonium Sulphate (THPS), 41331, Data Numbering Code: 8.2.2.2,8.2.2.3 Confidential Business Information

PMRA Document Number: 779589
Reference: 1996, Physical And Chemical Characteristics Of Tolcide PS200: Specific Gravity, Ph, Oxidizing Or Reducing And Viscosity., 120-30, Data Numbering Code: 3.5.6,3.5.7,3.5.8,3.5.9 Confidential Business Information

PMRA Document Number: 779590
Reference: 1997, Physical And Chemical Characteristics Of Tolcide PS200:, 120-31, Data Numbering Code: 3.5.14 Confidential Business Information

PMRA Document Number: 1111421
Reference: 1997, Tetrakis (Hydroxymethyl) Phosphonium Sulfate (THPS): Manufacturing Methods For The Technical Active, Wmc/rc-m0006a, Data Numbering Code: 2.11 Confidential Business Information

PMRA Document Number: 783361
Reference: 1997, Tetrakis (Hydroxymethyl) Phosphonium Sulfate (THPS): Preliminary Analysis Methodology/validation, Wmc/rc-m0006c, Data Numbering Code: 2.13.1 Confidential Business Information

PMRA Document Number: 783362
Reference: 1997, Tetrakis (Hydroxymethyl) Phosphonium Sulfate (THPS): Preliminary Analysis, Wmc/rc-m0006d, Data Numbering Code: 2.13.2,2.13.3,2.13.4 Confidential Business Information

PMRA Document Number: 783360
Reference: 1997, Tetrakis (Hydroxymethyl) Phosphonium Sulfate (THPS): Specifications, Wmc/rc-m0006b, Data Numbering Code: 2.12.1 Confidential Business Information

PMRA Document Number: 779587
Reference: 1997, US EPA, Product Chemistry : Tolcide® 200 Test Id, Data Numbering Code: 3.2.2,3.2.3,3.3,3.4 Confidential Business Information

PMRA Document Number: 907980
Reference: 2000, EPA Confidential Statement Of Formula, Data Numbering Code: 3.7 Confidential Business Information

PMRA Document Number: 1111447
Reference: 2002, Five Batch Analysis., Data Numbering Code: 2.13.3 Confidential Business Information

PMRA Document Number: 779586
Reference: 2003, Summary Of Applicant, Formulator And Product/chemical Information : Tolcide Ps200, Data Numbering Code: 3.1 Confidential Business Information

PMRA Document Number: 907982
Reference: 2003, Summary Of Applicant, Formulator And Product/chemical Information : Tolcide PS200, Data Numbering Code: 3.1 Confidential Business Information

PMRA Document Number: 783357
Reference: 2003, Summary Of Applicant, Manufacturer And Product/chemical Information, Data Numbering Code: 2.1,2.2,2.3,2.3.1,2.4,2.5,2.6,2.7,2.8,2.9 Confidential Business Information

PMRA Document Number: 783364
Reference: 2003, Summary Of Physical And Chemical Properties Of THPS, Data Numbering Code: 2.14 Confidential Business Information

PMRA Document Number: 783363
Reference: 2003, Summary Of Physical And Chemical Properties Of THPS-75%, Data Numbering Code: 2.14,2.16 Confidential Business Information

PMRA Document Number: 783415
Reference: 2003, Summary Of Physicochemical Properties., Data Numbering Code: 8.2.1

PMRA Document Number: 783418
Reference: 2003, Waiver Request For Analytical Methodology : Biota, Data Numbering Code: 8.2.2.4
PMRA Document Number: 783416
Reference: 2003, Waiver Request For Analytical Methodology : Sediment, Data Numbering Code: 8.2.2.2

PMRA Document Number: 908703
Reference: 2004, Analytical Methods For TetrakisHydroxymethyl Phosphonium Sulphate (THPS), 41331, Data Numbering Code: 8.2.2.3 Confidential Business Information

PMRA Document Number: 908704
Reference: 2004, Analytical Methods For TetrakisHydroxymethyl Phosphonium Sulphate (THPS), 41331, Data Numbering Code: 8.2.2.3 Confidential Business Information

PMRA Document Number: 908705
Reference: 2004, Analytical Methods For TetrakisHydroxymethyl Phosphonium Sulphate (THPS)., 41331, Data Numbering Code: 8.2.2.3 Confidential Business Information

PMRA Document Number: 1111448
Reference: 2004, Certified Analytical Standard Of The Active Ingredient. Certificate Of Analysis. Analytical Method To Confirm Assay (%w/w), Data Numbering Code: 2.15 Confidential Business Information

PMRA Document Number: 908702
Reference: Analytical Methods For TetrakisHydroxymethyl Phosphonium Sulphate (THPS)., 41331, Data Numbering Code: 8.2.2.3 Confidential Business Information

PMRA Document Number: 907790
Reference: Formulation Process., Data Numbering Code: 3.2,3.3,3.4,3.5 Confidential Business Information

PMRA Document Number: 907791
Reference: PMRA, Oxidising Or Reducing Agent., Data Numbering Code: 3.5.8 Confidential Business Information

PMRA Document Number: 779588
Reference: Summary of Physical and Chemical Properties of Tolcide PS200. Data Numbering Code 3.5. Confidential Business Information.

2.0 Human and Animal Health

PMRA Document Number: 910816
Reference: , Toxicology And Carcinogenesis Studies Of Tetrakis(hydroxymethyl) Phosphonium Sulfate (THPS) (CAS No. 55566-30-8) And Tetrakis(hydroxymethyl) Phosphonium Chloride (THPC) (CAS No. 124-64-1) In F344/n Rats And B6c3f1 Mice (gavage Studies), Data Numbering Code: 4.4.2,4.4.3,4.4.4

PMRA Document Number: 783375
Reference: 1985, Tetrakishydroxymethyl Phosphonium Sulfate (THPS): Acute Oral Toxicity To Rats (of DP 435). Data Numbering Code: 4.2.1

PMRA Document Number: 783461
Reference: 1985, U.S. EPA, Tetrakishydroxymethyl Phosphonium Sulphate (THPS): Acute Toxicity To Rats Of Dp 435, Data Numbering Code: 12.5.4

PMRA Document Number: 783469
Reference: 1987, U.S. EPA, Chronic Toxicity/carinogenicity (82-1, 83- 2, And 83-5), Data Numbering Code: 12.5.4

PMRA Document Number: 783377
Reference: 1989, Acute Dermal Toxicity To Rats Of THPS. Data Numbering Code: 4.2.2

PMRA Document Number: 1198185
Reference: 1989, Clarification On: Acute Inhalation Toxicity Study In Rats. Data Numbering Code: 4.2.3

PMRA Document Number: 1257992
Reference: 1989, DP 435: 28 Day Dermal Dose Range-finding Study In The Rat (Confidential Business Information Reference Document), Data Numbering Code: 4.3.4 Confidential Business Information

PMRA Document Number: 783385
Reference: 1989, DP 435: 28 Day Dermal Dose Range-finding Study In The Rat. Data Numbering Code: 4.3.4

PMRA Document Number: 1257990
Reference: 1989, DP 435: 28 Day Oral (gavage) Dose Rangefinding Study In The Rat (Confidential Business Information Reference Document), Data Numbering Code: 4.3.1
Confidential Business Information

PMRA Document Number: 783383
Reference: 1989, DP 435: 28 Day Oral (gavage) Dose Rangefinding Study In The Rat. Data Numbering Code: 4.3.1

PMRA Document Number: 783379
Reference: 1989, Irritant Effects On The Rabbit Eye Of THPS. Data Numbering Code: 4.2.4

PMRA Document Number: 783380
Reference: 1989, Irritant Effects On The Rabbit Skin Of THPS. Data Numbering Code: 4.2.5

PMRA Document Number: 908718
Reference: 1989, Lab Reference Alw/6/89. Data Numbering Code: 4.3.1

PMRA Document Number: 783398
Reference: 1989, Tetrakis(hydroxymethyl) Phosphonium Sulfate (THPS) .- Assessment Of Genotoxicity In An Unscheduled Dna Synthesis Assay Using Adult Rat Hepatocyte Primary Cultures, Data Numbering Code: 4.5.5

PMRA Document Number: 783402
Reference: 1989, Tetrakis(hydroxymethyl) Phosphonium Sulfate (THPS) : Chromosomal Aberrations Assay With Chinese Hamster Ovary Cells In Vitro. Data Numbering Code: 4.5.6

PMRA Document Number: 783397
Reference: 1989, Tetrakis(hydroxymethyl) Phosphonium Sulfate (THPS) Testing For Mutagenic Activity With Salmonella Typhimurium Ta 1535, Ta 1537, Ta 1538, Ta 98 And Ta 100. Data Numbering Code: 4.5.4

PMRA Document Number: 783378
Reference: 1989, THPS: Acute Inhalation Toxicity Study In Rats. Data Numbering Code: 4.2.3

PMRA Document Number: 783468
Reference: 1989, U.S. EPA, 28-day Dermal Range-finding Study, Data Numbering Code: 12.5.4

PMRA Document Number: 783463
Reference: 1989, U.S. EPA, Acute Dermal/rats (81-2), Data Numbering Code: 12.5.4

PMRA Document Number: 783464
Reference: 1989, U.S. EPA, Acute Inhalation/rats (81-3), Data Numbering Code: 12.5.4

PMRA Document Number: 783477
Reference: 1989, U.S. EPA, Mutagenicity: In Vitro Unscheduled Dna Synthesis Assay In Primary Rat Hepatocytes, Data Numbering Code: 12.5.4

PMRA Document Number: 783465
Reference: 1989, U.S. EPA, Primary Eye Irritation/rabbits (81-4), Data Numbering Code: 12.5.4

PMRA Document Number: 783466
Reference: 1989, U.S. EPA, Primary Skin Irritation/rabbits (81-5), Data Numbering Code: 12.5.4

PMRA Document Number: 783476
Reference: 1989, U.S. EPA, Salmonella And Escherichia Coli/mammalian Activation Gene Mutation Assay (84-2(a)), Data Numbering Code: 12.5.4

PMRA Document Number: 1257989
Reference: 1990, Dp 435: 13 Week Oral (gavage) Toxicity Study In The Rat (Confidential Business Information Reference Document), Data Numbering Code: 4.3.1 Confidential Business Information

PMRA Document Number: 783382
Reference: 1990, Dp 435: 13 Week Oral (gavage) Toxicity Study In The Rat. Alw/4/90, MRID: 44135403, Data Numbering Code: 4.3.1

PMRA Document Number: 783412
Reference: 1990, Tris Hydroxy Methyl Phosphine Oxide: Acute Oral Toxicity Study In The Rat. Data Numbering Code: 4.8

PMRA Document Number: 908701
Reference: 1990, Tris Hydroxy Methyl Phosphine Oxide: Acute Oral Toxicity Study In The Rat. Data Numbering Code: 4.8

PMRA Document Number: 1257998
Reference: 1991, THPS: Oral (gavage) Range-finding In The Pregnant Rabbit (Confidential Business Information Reference Document), Data Numbering Code: 4.5.3 Confidential Business Information

PMRA Document Number: 783395
Reference: 1991, THPS: Oral (Gavage) Range-finding In The Pregnant Rabbit. Data Numbering Code: 4.5.3

PMRA Document Number: 1257996
Reference: 1991, THPS: Oral (gavage) Range-finding In The Regnant Rat (Confidential Business Information Reference Document0, Data Numbering Code: 4.5.2 Confidential Business Information

PMRA Document Number: 783393
Reference: 1991, THPS: Oral (gavage) Range-finding In The Regnant Rat. Data Numbering Code: 4.5.2

PMRA Document Number: 1257999
Reference: 1991, THPS: Oral (gavage) Teratology Study In The Rabbit (Confidential Business Information Reference Document), Data Numbering Code: 4.5.3 Confidential Business Information

PMRA Document Number: 783396
Reference: 1991, THPS: Oral (gavage) Teratology Study In The Rabbit. Data Numbering Code: 4.5.3

PMRA Document Number: 1257997
Reference: 1991, THPS: Oral (Gavage) Teratology Study In The Rat (Confidential Business Information Reference Document), Data Numbering Code: 4.5.2. Confidential Business Information

PMRA Document Number: 783394
Reference: 1991, THPS: Oral (Gavage) Teratology Study In The Rat. Data Numbering Code: 4.5.2

PMRA Document Number: 783475
Reference: 1991, U.S. EPA, Teratology Developmental Toxicity/rabbit (83-3b), Data Numbering Code: 12.5.4

PMRA Document Number: 783474
Reference: 1991, U.S. EPA, Teratology Developmental Toxicity/rabbit (83-3b). Data Numbering Code: 12.5.4

PMRA Document Number: 783471
Reference: 1991, U.S. EPA, Teratology Developmental Toxicity/rat (83-3a), Data Numbering Code: 12.5.4

PMRA Document Number: 783470
Reference: 1991, U.S. EPA, Teratology Developmental Toxicity/rat (83-3a). Data Numbering Code: 12.5.4

PMRA Document Number: 783459
Reference: 1992, U.S. EPA, New Chemical Screen For Tetrakis (hydroxymethyl) Phosphonium Sulphate (THPS) US EPA Memorandum Dated May 28, 1992. Data Numbering Code: 12.5.4

PMRA Document Number: 783460
Reference: 1993, U.S. EPA, THPS Review Of Toxicity Data US EPA Memorandum Dated Sep 16, 1993. Data Numbering Code: 12.5.4

PMRA Document Number: 783399
Reference: 1994, Supplemental Information For Report MRID No. 42236317: THPS 75% - Assessment Of Genotoxicity In An Unscheduled Dna Ynthesis Assay Using Adult Rat Hepatocyte Primary Cultures (supplemental Report To Dec. 22, 1989. Data Numbering Code: 4.5.5

PMRA Document Number: 783381
Reference: 1994, Tolcide THPS 75%: Magnusson & Kligman Maximisation Study In The Guinea Pig. Data Numbering Code: 4.2.6

PMRA Document Number: 783376
Reference: 1994, Tolcide THPS PS75%: Acute Oral Toxicity Test In The Rat. Data Numbering Code: 4.2.1

PMRA Document Number: 783462
Reference: 1994, U.S. EPA, Acute Oral/rats (81-1) DP Barcode D205699 Us Epa Der Dated. Data Numbering Code: 12.5.4

PMRA Document Number: 783467
Reference: 1994, U.S. EPA, Dermal Sensitization (81-6), Data Numbering Code: 12.5.4

PMRA Document Number: 783479
Reference: 1994, U.S. EPA, Response To Supplementary Information For Chemical THPS Dp Barcode D205884 And D209332 US EPA Memorandum Dated Nov 29, 1994. Data Numbering Code: 12.5.4

PMRA Document Number: 783487
Reference: 1994, U.S. EPA, THPS EPA File Symbol No. 33677-G, Data Numbering Code: 12.5.4

PMRA Document Number: 908709
Reference: 1995, THPO: Twenty-eight Day Sub-acute Dermal Toxicity Study In The Rat. Data Numbering Code: 4.8

PMRA Document Number: 908692
Reference: 1995, THPS: Mouse Lymphoma Mutation Assay. Data Numbering Code: 4.5.5

PMRA Document Number: 783482
Reference: 1995, U.S. EPA, THPS Dla Protocol Review, Data Numbering Code: 12.5.4

PMRA Document Number: 783478
Reference: 1995, U.S. EPA, THPS: EPA File Symbol 33677-G US EPA, Data Numbering Code: 12.5.4
PMRA Document Number: 783488
Reference: 1995, U.S. EPA, Toxicology Endpoint Selection Document, Data Numbering Code: 12.5.4

PMRA Document Number: 783490
Reference: 1996, Product Registration Recommendation Sheet : Tolcide PS75, Data Numbering Code: 12.5.4

PMRA Document Number: 783494
Reference: 1996, Submission Of Studies Under Fifra 6(a)(2) Acute Inhalation Studies For PS352C And PS355A, Data Numbering Code: 12.5.4

PMRA Document Number: 783413
Reference: 1996, THPO: Twenty-eight Day Sub-acute Dermal Toxicity Study In The Rat. Data Numbering Code: 4.8

PMRA Document Number: 783406
Reference: 1996, THPS Paper Leachate Pl101: Reverse Mutation In Five Histidine-requiring Strains Of Salmonella Typhimurium. Data Numbering Code: 4.5.8

PMRA Document Number: 783400
Reference: 1996, THPS: Mouse Lymphoma Mutation Assay. Data Numbering Code: 4.5.5

PMRA Document Number: 783403
Reference: 1996, THPS: Oral (gavage) Dominant Lethal Study In The Rat. Data Numbering Code: 4.5.7

PMRA Document Number: 1258000
Reference: 1996, THPS: Oral (gavage) Dominant Lethal Study In The Rat. Data Numbering Code: 4.5.7 Confidential Business Information

PMRA Document Number: 783409
Reference: 1996, Trishydroxymethyl Phosphine Oxide (THPO): Mutation At The Thymidine Kinase (tk) Locus Of Mouse Lymphoma L5178y Cells Using The Microtitre Fluctuation Technique. Data Numbering Code: 4.5.8

PMRA Document Number: 908698
Reference: 1996, Trishydroxymethyl Phosphine Oxide (THPO): Mutation At The Thymidine Kinase (tk) Locus Of Mouse Lymphoma L5178y Cells Using The Microtitre Fluctuation Technique. Data Numbering Code: 4.5.8

PMRA Document Number: 783407
Reference: 1996, Trishydroxymethyl Phosphine Oxide: Induction Of Chromosome Aberrations In Cultured Chinese Hamster Ovary (CHO) Cells. Data Numbering Code: 4.5.8

PMRA Document Number: 908696
Reference: 1996, Trishydroxymethyl Phosphine Oxide: Induction Of Chromosome Aberrations In Cultured Chinese Hamster Ovary (cho) Cells. Data Numbering Code: 4.5.8

PMRA Document Number: 783408
Reference: 1996, Trishydroxymethyl Phosphine Oxide: Reverse Mutation In Four Histidine-Requiring Strains Of Salmonella Typhimurium And One Strain Of Tryptophan-requiring Strain Of Escherichia Coli, Data Numbering Code: 4.5.8

PMRA Document Number: 908697
Reference: 1996, Trishydroxymethyl Phosphine Oxide: Reverse Mutation In Four Histidine Requiring Strains Of Salmonella Typhimurium And One Strain Of Tryptophan-requiring Strain Of Escherichia Coli. Data Numbering Code: 4.5.8

PMRA Document Number: 783481
Reference: 1996, U.S. EPA, In Vivo Mammalian Cytogenetics Dominant Lethal Test In Rats; Data Numbering Code: 12.5.4

PMRA Document Number: 783483
Reference: 1996, U.S. EPA, Mammalian Cells In Culture Gene Mutation Assay In Mouse Lymphoma (l5178) Cells. Data Numbering Code: 12.5.4

PMRA Document Number: 783485
Reference: 1996, U.S. EPA, Mammalian Cells In Culture Gene Mutation Assay In Mouse Lymphoma L5178y. Data Numbering Code: 12.5.4

PMRA Document Number: 783484
Reference: 1996, U.S. EPA, Mammalian Cells In Culture, Chromosome Aberrations In Cho Cells. Data Numbering Code: 12.5.4

PMRA Document Number: 783486
Reference: 1996, U.S. EPA, Reverse Gene Mutation In Salmonella Typhimurium (oppts 870.5265) And E Coli (oppts 870.5100)/both With Mammalian Activation [84-2], Data Numbering Code: 12.5.4

PMRA Document Number: 907803
Reference: 1997, Reply To Deficiency Letter Dated 19 July 2004. Data Numbering Code: 5.8

PMRA Document Number: 908700
Reference: 1997, Revised: See Additional Report Requested By PMRA: THPS:preliminary Investigation Of Metabolismin The Rat. Data Numbering Code: 4.5.9

PMRA Document Number: 783480
Reference: 1998, U.S. EPA, THPS: EPA Reg. No. 33677-7 US EPA, Data Numbering Code: 12.5.4

PMRA Document Number: 783492
Reference: 1998, U.S. EPA, THPS: Review Of Data Submitted Under 6(a)(2), Data Numbering Code: 12.5.4

PMRA Document Number: 783491
Reference: 1998, U.S. EPA, THPS: Submission Of A Subchronic Toxicity Study, Data Numbering Code: 12.5.4

PMRA Document Number: 783410
Reference: 1999, (14c)-THPS: A Study Of Absorption, Istribution, Metabolism And Excretion Following Oral Administration To The Rat. Data Numbering Code: 4.5.9

PMRA Document Number: 1258001
Reference: 1999, (14c)-THPS: A Study Of Absorption, Istribution, Metabolism And Excretion Following Oral Administration To The Rat. Data Numbering Code: 4.5.9 Confidential Business Information

PMRA Document Number: 908699
Reference: 1999, 14c THPS: A Study Of Absorption, Distribution, Metabolism And Excretion Following Oral Administration To The Rat. Data Numbering Code: 4.5.9

PMRA Document Number: 1196486
Reference: 1999, Determination Of THPS Degradation Route In Pulp (appendix 1) , Data Numbering Code: 5.2

PMRA Document Number: 1286994
Reference: 1999, Request For Clarification 260506#3: THPS: Oral Gavage Two Generation Reproduction Study In The Rat. Data Numbering Code: 4.5.1

PMRA Document Number: 1196493
Reference: 1999, Summary Of Results From THPS Exposure Study, Method Am6265, Data Numbering Code: 5.2

PMRA Document Number: 910658
Reference: 1999, Summary Of Test Data To Support The Use Of Tetrakis (hydroxymethyl) Phosphium Sulfate (THPS) As A Slimicide In The Manufacture Of Food Contact Paper And Paperboard And As An Emulsion Preservative. Data Numbering Code: 4.8

PMRA Document Number: 908725
Reference: 1999, Supplemental Information To THPS : Oral Gavage Two Generation Reproduction Study In The Rat . Data Numbering Code: 4.5.1

PMRA Document Number: 783404
Reference: 1999, Supplemental Report To THPS: Oral (gavage) Dominant Lethal Study In The Rat, Data Numbering Code: 4.5.7

PMRA Document Number: 783401
Reference: 1999, Supplemental Report To THPS. Data Numbering Code: 4.5.5

PMRA Document Number: 1257994
Reference: 1999, THPS: Oral Gavage Two Generation Reproduction Study In The Rat, Data Numbering Code: 4.5.1 Confidential Business Information

PMRA Document Number: 1257995
Reference: 1999, THPS: Oral Gavage Two Generation Reproduction Study In The Rat, 1169/001, MRID: 45320801, Data Numbering Code: 4.5.1 Confidential Business Information

PMRA Document Number: 783391
Reference: 1999, THPS: Oral Gavage Two Generation Reproduction Study In The Rat. (report Pages 1 - 227), Data Numbering Code: 4.5.1

PMRA Document Number: 1257993
Reference: 1999, THPS: Oral Gavage Two Generation Reproduction Study In The Rat. Data Numbering Code: 4.5.1 Confidential Business Information

PMRA Document Number: 783489
Reference: 1999, U.S. EPA, THPS: Risk Assessment For Use Of The Active Ingredient In Manufacture Of Food Contact Paper. Data Numbering Code: 12.5.4

PMRA Document Number: 1258002
Reference: 2000, (14c)-THPS: Identification Of Metabolites In The Rat. Data Numbering Code: 4.5.9 Confidential Business Information

PMRA Document Number: 783411
Reference: 2000, (14c)-THPS: Identification Of Metabolites In The Rat, 254/55, Data Numbering Code: 4.5.9

PMRA Document Number: 1198179
Reference: 2000, Certificate Of Analysis. Batch X27j1, Cems-1223, Data Numbering Code: 4.8 Confidential Business Information

PMRA Document Number: 1198180
Reference: 2000, PS75 Part 4 Questions 8 & 9 (excel Document), Cems-1223, Data Numbering Code: 4.2,4.3,4.4,4.5,4.6

PMRA Document Number: 783405
Reference: 2000, THPS: Micronucleus Test In The Mouse, Data Numbering Code: 4.5.7

PMRA Document Number: 908695
Reference: 2000, THPS: Micronucleus Test In The Mouse. Data Numbering Code: 4.5.7

PMRA Document Number: 783493
Reference: 2001, U.S. EPA, THPS: Review Of Two-generation Reproduction Study In Rats, Data Numbering Code: 12.5.4

PMRA Document Number: 1196487
Reference: 2002, Hplc Method For The Determination Of Trishydroxymethylphosphine Oxide In Water (appendix 2) , Method Am6265, Data Numbering Code: 5.2 Confidential Business Information

PMRA Document Number: 783495
Reference: 2002, Reportable Information Under Fifra 6(a)(2):, Data Numbering Code: 12.5.4

PMRA Document Number: 783392
Reference: 2002, Supplemental Information To THPS: Oral Gavage Two Generation Reproduction Study In The Rat. Supplement To 1169/001, Data Numbering Code: 4.5.1

PMRA Document Number: 783390
Reference: 2003, Additional Information On NTP TR 296, Data Numbering Code: 4.4.4

PMRA Document Number: 912540
Reference: 2003, Justification And Waiver Request For Additional In Vivo Genotoxicity Test, Data Numbering Code: 4.5.7

PMRA Document Number: 783374
Reference: 2003, Summary Of Toxicology : Tolcide PS75 . Data Numbering Code: 4.1

PMRA Document Number: 908720
Reference: 2003, Summary Of Toxicology : Tolcide PS75. Data Numbering Code: 4.1

PMRA Document Number: 908234
Reference: 2003, Summary. Data Numbering Code: 4.1

PMRA Document Number: 783384
Reference: 2003, Waiver Request For Short-term Dermal (90 Day) . Data Numbering Code: 4.3.4

PMRA Document Number: 907801
Reference: 2004, Reply To Deficiency Letter Dated 19 July 2004. THPS. Potential Human Exposure During Use. Rhodia Internal Report. Data Numbering Code: 5.2

PMRA Document Number: 908719
Reference: 2004, The Equilibrium Of THPS With Formaldehyde. Rhodia Internal Report. . Data Numbering Code: 4.1

PMRA Document Number: 908726
Reference: 2004, THPS: Oral (gavage) Teratology Study In The Rat. Data Numbering Code: 4.5.2
PMRA Document Number: 1456285
Reference: 2004, Tolcide PS Exposure Study Paper Manufacture - Leipa, Schwedt, Germany, Data Numbering Code: 5.2 Confidential Business Information

PMRA Document Number: 908716
Reference: 2004, Tolcide THPS 75%: Magnusson & Kligman Maximisation Study In The Guinea Pig. Data Numbering Code: 4.2.6

PMRA Document Number: 908710
Reference: 2004, Tris Hydroxy Methyl Phosphine Oxide: Acute Oral Toxicity Study In Rats, Data Numbering Code: 4.8

PMRA Document Number: 1258003
Reference: 2004, Tris Hydroxy Methyl Phosphine Oxide: Acute Oral Toxicity Study In The Rat. Data Numbering Code: 4.8 Confidential Business Information

PMRA Document Number: 1192048
Reference: 2006, In Vivo Dermal Absorption Of 14 C-THPS Formulated As Tolcide PS75 And As Tolcide PS75 E In The Male Rat. Includes 4 Page First Amendement To Report. A19225, Data Numbering Code: 5.8

PMRA Document Number: 1403047
Reference: 2006, In Vivo Dermal Absorption Of 14 C-THPS Formulated As Tolcide PS75 And As Tolcide PS75 E In The Male Rat. Includes 4 Page First Amendement To Report. A19225, Data Numbering Code: 5.8 Confidential Business Information

PMRA Document Number: 1191994
Reference: 2006, Response To E-mail Dated 29 March 2006 Requesting The Dermal Absorption Report. Data Numbering Code: 5.8

PMRA Document Number: 1306378
Reference: 2006, Rhodia Response - Oral Gavage Two Generation Reproduction Study In The Rat. Data Numbering Code: 4.5.1

PMRA Document Number: 1192036
Reference: 2006, Stability Of 14 C Labelled THPS Formulated As Tolcide PS75 And As Tolcide PS75 E, Data Numbering Code: 5.8

PMRA Document Number: 1403046
Reference: 2006, Stability Of 14 C Labelled THPS Formulated As Tolcide PS75 And As Tolcide PS75 E, Data Numbering Code: 5.8 Confidential Business Information

PMRA Document Number: 1371758
Reference: 2007, PMRA Meeting On THPS - 30 January 07 - # 2- Rhodia Powerpoint Presentation "PMRA Submissions 2003-1429/1432/1433. Tolcide PS75, Tolcide PS75-lt & Tolcide 200", Data Numbering Code: 4.8

PMRA Document Number: 1410697
Reference: 2007, THPS: Oral Gavage Two Generation Reproduction Study In The Rat: Rhodia Response To PMRA Study Review, Addressing Study Deficiencies And Providing Interpretation, 1169/001, Data Numbering Code: 4.5.1

PMRA Document Number: 908712
Reference: Acute Dermal Toxicity To Rats Of THPS. Data Numbering Code: 4.2.2

PMRA Document Number: 1288017
Reference: Bailey G. et al, 2006, Abstract: 'Well Bred, Well Fed, But Dead': The Influence Of Diet On The Post-natal Survival Of The Sprague Dawley Rat. Data Numbering Code: 4.5.1

PMRA Document Number: 1288352
Reference: Control Data For One Generation Reproduction Studies 1997 - 2002 - Oral Gavage One Generation Reproduction Study In The Rat With Evaluation Of Subchronic Toxicity, Data Numbering Code: 4.5.1

PMRA Document Number: 1288357
Reference: Control Data For One Generation Reproduction Studies 1997 - 2002 - Oral Gavage One Generation Reproduction Study In The Rat With Evaluation Of Subchronic Toxicity, Data Numbering Code: 4.5.1

PMRA Document Number: 1288353
Reference: Control Data For One Generation Reproduction Studies 1997 - 2002 - Oral Gavage One Generation Reproduction Study In The Rat, Data Numbering Code: 4.5.1

PMRA Document Number: 1288354
Reference: Control Data For One Generation Reproduction Studies 1997 - 2002 - Oral Gavage One Generation Reproduction Study In The Rat, Data Numbering Code: 4.5.1

PMRA Document Number: 1288356
Reference: Control Data For One Generation Reproduction Studies 1997 - 2002 - Oral Gavage One Generation Reproduction Study In The Rat, Data Numbering Code: 4.5.1

PMRA Document Number: 1288362
Reference: Control Data For One Generation Reproduction Studies 1997 - 2002 - Oral Gavage One Generation Reproduction Study In The Rat, Data Numbering Code: 4.5.1

PMRA Document Number: 1288355
Reference: Control Data For Two Generation Reproduction Studies 1997 - 2002 - Dietary Two Generation Reproduction Study In The Rat, Data Numbering Code: 4.5.1

PMRA Document Number: 1288358
Reference: Control Data For Two Generation Reproduction Studies 1997 - 2002 - Dietary Two Generation Reproduction Study In The Rat, Data Numbering Code: 4.5.1

PMRA Document Number: 1288361
Reference: Control Data For Two Generation Reproduction Studies 1997 - 2002 - Dietary Two Generation Reproduction Study In The Rat, Data Numbering Code: 4.5.1

PMRA Document Number: 1288359
Reference: Control Data For Two Generation Reproduction Studies 1997 - 2002 - Oral Gavage Two Generation Reproduction Study In The Rat, Data Numbering Code: 4.5.1

PMRA Document Number: 1288360
Reference: Control Data For Two Generation Reproduction Studies 1997 - 2002 - Oral Gavage Two Generation Reproduction Study In The Rat, Data Numbering Code: 4.5.1

PMRA Document Number: 908717
Reference: DP 435: 13 Week Oral (gavage) Toxicity Study In The Rat. Data Numbering Code: 4.3.1

PMRA Document Number: 908732
Reference: DP 435: 28 Day Dermal Dose Range Finding Study In The Rat. Data Numbering Code: 4.3.4

PMRA Document Number: 1221555
Reference: Incidence Of 3 Tumours In Untreated Control Groups In B6c3f1 Mice - NTP Historical Control Data Base (malignant Lymphomas, Adrenal Pheochromocytomas, Endometrial Stromal Polyps) (excel Document), Data Numbering Code: 4.4.1

PMRA Document Number: 908714
Reference: Irritant Effects On The Rabbit Eye Of THPS. Data Numbering Code: 4.2.4

PMRA Document Number: 908715
Reference: Irritant Effects On The Rabbit Skin Of THPS. Data Numbering Code: 4.2.5

PMRA Document Number: 783389
Reference: Jameson C. et al, 1980, Toxicology And Carcinogenesis Studies Of Tetrakis(hydroxymethyl) Phosphonium Sulfate (THPS) (cas No. 55566-30-8) And Tetrakis(hydroxymethyl) Phosphonium Chloride (THPC) (cas No. 124-64-1) In F344/n Rats And B6c3f1 Mice (Gavage Studies). Data Numbering Codes: 4.4.2,4.4.3,4.4.4

PMRA Document Number: 783387
Reference: Jameson C. et al, 1987, Carcinogenesis in F344/N Rats in Toxicology and Carcinogenesis Studies Of Tetrakis(Hydroxymethyl) Phosphonium Sulfate (THPS) (CAS No. 55566-30-8) and Tetrakis(Hydroxymethyl) Phosphonium Chloride (THPC) (CAS No. 124-64-1) in F344/N Rats and B6C3F1 Mice (Gavage tudies) National Toxicology Program, Research Triangle Park, NC NTP Technical Report 296, NIH Publication No. 87-2552. Data Numbering Code: 4.4.2

PMRA Document Number: 910822
Reference: Jameson C. et al, Carcinogenesis in F344/N Rats in Toxicology and Carcinogenesis Studies Of Tetrakis(Hydroxymethyl) Phosphonium Sulfate (THPS) (CAS No. 55566-30-8) and Tetrakis(Hydroxymethyl) Phosphonium Chloride (THPC) (CAS No. 124-64-1) in F344/N Rats and B6C3F1 Mice (Gavage tudies). Data Numbering Code: 4.4.1

PMRA Document Number: 1287089
Reference: Kurihara, H. et al, 2000, Changes With Sexual Maturation Of The Sperm Analytical Parameters In CRJ: CD(SD)IGS Rats. Data Numbering Code: 4.5.1

PMRA Document Number: 1288363
Reference: Multi-generation Reproduction Study Request For Clarification Dated July 24, 2006, Data Numbering Code: 4.5.1

PMRA Document Number: 1196431
Reference: Part 5 - Exposure (occupational And/or Bystander).reply To Deficiency Letter Dated 7 March 2006, Data Numbering Code: 5.2

PMRA Document Number: 907802
Reference: Reply To Deficiency Letter Dated 19 July, Data Numbering Code: 5.3,5.4,5.5

PMRA Document Number: 908733
Reference: Revised: Waiver, Data Numbering Code: 4.3.6

PMRA Document Number: 1032439
Reference: Short-term Dermal (28-day)& Multigeneration-reproduction (rodent). Data Numbering Code: 4.3.4,4.5.1

PMRA Document Number: 1288018
Reference: Table 4 Historical Control Data - Reproduction Studies With Sprague-dawley IGS CD Rat (1997 - 2002), Data Numbering Code: 4.5.1

PMRA Document Number: 908693
Reference: Tetrakis(hydroxymethyl) Phosphonium Sulfate (THPS) : Chromosomal Aberrations Assay With Chinese Hamster Ovary Cells In Vitro. Data Numbering Code: 4.5.6
PMRA Document Number: 908730

Reference: Tetrakis(hydroxymethyl) Phosphonium Sulfate (THPS) Testing For Mutagenic Activity With Salmonella Typhimurium Ta 1535, Ta 1537, Ta 1538, Ta 98 And Ta 100. Data Numbering Code: 4.5.4

PMRA Document Number: 908731
Reference: Tetrakis(hydroxymethyl) Phosphonium Sulfate (THPS). Assessment Of Genotoxicity In An Unscheduled Dna Synthesis Assay Using Adult Rat Hepatocyte Primary Cultures. Data Numbering Code: 4.5.5

PMRA Document Number: 908721
Reference: Tetrakishydroxymethyl Phosphonium Sulfate (THPS): Acute Oral Toxicity To Rats (of DP 435). Data Numbering Code: 4.2.1

PMRA Document Number: 908713
Reference: THPS: Acute Inhalation Toxicity Study In Rats. Data Numbering Code: 4.2.3

PMRA Document Number: 908694
Reference: THPS: Oral (gavage) Dominant Lethal Study In The Rat. Data Numbering Code: 4.5.7

PMRA Document Number: 908729
Reference: THPS: Oral (gavage) Range-finding In The Pregnant Rabbit. Data Numbering Code: 4.5.3

PMRA Document Number: 908727
Reference: THPS: Oral (gavage) Range-finding In The Pregnant Rat. Data Numbering Code: 4.5.2

PMRA Document Number: 908728
Reference: THPS: Oral (gavage) Teratology Study In The Rabbit. Data Numbering Code: 4.5.3

PMRA Document Number: 910818
Reference: THPS: Oral Gavage Two Generation Reproduction Study In The Rat. (report Pages 228 - 455). Data Numbering Code: 4.5.1

PMRA Document Number: 910820
Reference: THPS: Oral Gavage Two Generation Reproduction Study In The Rat. (report Pages 456 - 677), Data Numbering Code: 4.5.1

PMRA Document Number: 908724
Reference: THPS: Oral Gavage Two Generation Reproduction Study In The Rat. Data Numbering Code: 4.5.1

PMRA Document Number: 908722
Reference: Tolcide THPS PS75: Acute Oral Toxicity Test In The Rat. Data Numbering Code: 4.2.1

PMRA Document Number: 908734
Reference: Two year (gavage) studies in rats and mice in Toxicology and Carcinogenesis Studies Of Tetrakis(Hydroxymethyl) Phosphonium Sulfate (THPS) (CAS No. 55566-30-8) and Tetrakis(Hydroxymethyl) Phosphonium Chloride (THPC) (CAS No. 124-64-1) in F344/N Rats and B6C3F1 Mice (Gavage Studies). Data Numbering Codes: 4.4.1,4.4.2,4.4.3,4.4.4

PMRA Document Number: 1288019
Reference: Willoughby, C. And Bootomley, A. 1998, Variability In Offspring Surival And Reproductive Parameters In Recent Pre- And Postnatal And Multigeneration Studies In The CRL:CD (SD) IGS Rat. Data Numbering Code: 4.5.1

PMRA Document Number: 1286995
Reference: Willoughby, C. et al, 2000, A Study Of The Effects On Reproductive Performance In CRL:CD (SD) IGS Rats Fed A Variety Of Rodent Diets. Data Numbering Code: 4.5.1

3.0 Environment

PMRA Document Number: 783420
Reference: 1991, THPS: Determination Of Hydrolysis, Data Numbering Code: 8.2.3.2

PMRA Document Number: 783423
Reference: 1996, Aerobic Aquatic Metabolism Of 14c- Tetrakishydroxymethyl Phosphonium Sulphate (THPS) .Data Numbering Code: 8.2.3.5.4

PMRA Document Number: 783424
Reference: 1997, Anaerobic Aquatic Metabolism Of 14c- Tetrakishydroxymethyl Phosphonium Sulphate (THPS). Data Numbering Code: 8.2.3.5.6

PMRA Document Number: 783426
Reference: 2000, Soil/sediment Adsorption-desorption Of 14c-tetrakishydroxymethyl Phosphonium Sulphate (THPS), Data Numbering Code: 8.2.4.2

PMRA Document Number: 783431
Reference: 1989, THPS: Acute Toxicity To Daphnia Magna, Data Numbering Code: 9.3.2

PMRA Document Number: 783432
Reference: 1991, Tris (hydroxymethyl) Phosphonium Oxide (THPO): Acute Toxicity To Daphnia Magna, Data Numbering Code: 9.3.2

PMRA Document Number: 783433
Reference: 1990, THPS: Daphnia Magna 21 Day Juvenile Production Test Under Semistatic Conditions, Data Numbering Code: 9.3.3

PMRA Document Number: 783435
Reference: 1995, Acute Toxicity Of Tetrakis (hydroxymethyl) Phosphonium Sulfate (THPS) To The Mysid, (mysidopsis Bahia), Under Flow-through Conditions, Data Numbering Code: 9.4.2

PMRA Document Number: 783443
Reference: 1995, Acute Flow Through Mollusc Shell Deposition Test With Tetrakis (hydroxymethyl) Phosphonium Sulfate (THPS). Data Numbering Code: 9.4.4

PMRA Document Number: 783445
Reference: 1990, THPS: Acute Toxicity To Rainbow Trout. Data Numbering Code: 9.5.2.1

PMRA Document Number: 783446
Reference: 1991, Tris (hydroxymethyl) Phosphonium Oxide (THPO): Acute Toxicity To Rainbow Trout, Data Numbering Code: 9.5.2.1

PMRA Document Number: 783447
Reference: 1989, THPS: Acute Toxicity To Bluegill Sunfish. Data Numbering Code: 9.5.2.2

PMRA Document Number: 783450
Reference: 1995, Acute Toxicity Of Tetrakis (hydroxymethyl) Phosphonium Sulphate (THPS) To The Sheepshead Minnow, Cyprinodon Variegates, Under Fow-through Conditions. Data Numbering Code: 9.5.2.4

PMRA Document Number: 783452
Reference: 1987, THPS: The Acute Oral Toxicity (LD50) Of DP435 To The Mallard Duck. Data Numbering Code: 9.6.2.2

PMRA Document Number: 783453
Reference: 1987, THPS: The Dietary Toxicity (LC50) Of DP435 To The Bobwhite Quail. Data Numbering Code: 9.6.2.4

PMRA Document Number: 783454
Reference: 1987, THPS: The Dietary Toxicity (LC50) Of DP435 To The Mallard Duck. Data Numbering Code: 9.6.2.5

PMRA Document Number: 783456
Reference: 1989, HPS: Determination Of Its EC50 To Selenastrum Carpricornutum Under Non-Axenic Conditions . Data Numbering Code: 9.8.2

PMRA Document Number: 783458
Reference: 1990, Determination Of Environmental Fate Of THPS In Water Treatment Applications. Data Numbering Code: 8.6,9.9 Confidential Business Information

PMRA Document Number: 783473
Reference: 2001, Tolcide PS75: Lemna Growth Inhibition Test. Data Numbering Code: 9.8.5

PMRA Document Number: 908708
Reference: 1995, Revised: 14C THPS : Photodegradation In Sterile,aqueous Solution. Data Numbering Code: 8.2.3.3.2

4.0 Value

PMRA Document Number: 908254
Reference: Efficacy And Summary Of Studies, Data Numbering Code: 10.1,10.2.3

PMRA Document Number: 908255
Reference: 2004, Description Of Pest Problem, Data Numbering Code: 10.2.2

PMRA Document Number: 908256
Reference: 2004, Evaluation Of Tolcide PS75 Performance Against Laboratory Generated Biofilm. Data Numbering Code: 10.2.3.2

PMRA Document Number: 908257
Reference: 2004, Quantitative Suspension Test Method (qst). Data Numbering Code: 10.2.3.2

PMRA Document Number: 908258
Reference: 2004, Evaluation Of Tolcide PS75 For Control Of Bacteria In A Cooling Water System. Data Numbering Code: 10.2.3.2

PMRA Document Number: 908259
Reference: 2004, Performance Of Tolcide PS75 Against Fresh Water Algal Species. Data Numbering Code: 10.2.3.2

PMRA Document Number: 908260
Reference: 2004, Anti-microbial Performance Of Tolcide. PS75e Under Typical White Water Conditions Using Calmex Isolates. Data Numbering Code: 10.2.3.2

PMRA Document Number: 908261
Reference: 2004, Anti-microbial Performance Of Tolcide PS75e Under Typical White Water Conditions Using Tipco Isolates, Data Numbering Code: 10.2.3.2

PMRA Document Number: 1257939
Reference: 2006, Efficacy And Summary Of Studies.(Confidential Business Information Reference Document), Data Numbering Code: 10.1,10.2.3 Confidential Business Information

PMRA Document Number: 1257940
Reference: 2004, Evaluation Of Tolcide PS75 Performance Against Laboratory Generated Biofilm. Data Numbering Code: 10.2.3.2 Confidential Business Information

PMRA Document Number: 1257943
Reference: 2004, Anti-microbial Performance Of Tolcide PS75e Under Typical White Water Using Tipco Isolates, Data Numbering Code: 10.2.3.2 Confidential Business Information

B. Additional Information Considered

i) Published Information

1.0 Human and Animal Health

PMRA Document Number: 1440847
Reference: International Programme On Chemical Safety Environmental Health Criteria 89, Formaldehyde. Data Numbering Code: 4.8

PMRA Document Number: 1440848
Reference: United Nations Environment Programme International Labour Organization World Health Organization - International Programme on Chemical Safety Environmental Health Criteria 218, Flame retardants: tris (2-butoxyethyl) phosphate, tris (2-ethylhexyl) phosphate and tetrakis (hydroxymethyl) phosphonium salts. Data Numbering Code: 4.8

PMRA Document Number: 1440849
Reference: 2004, Tetrakishydroxymethylphosphonium Sulfate (thps) 75% Aq. Sol: Acute Inhalation Toxicity (nose Only) Study In The Rat, Data Numbering Code: 4.2.3