Screening Assessment for the Challenge

Thiourea

Chemical Abstracts Service Registry Number
62-56-6

Environment Canada
Health Canada

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Synopsis

Pursuant to section 74 of the *Canadian Environmental Protection Act*, 1999 (CEPA 1999), the Ministers of the Environment and of Health have conducted a screening assessment of thiourea, Chemical Abstracts Service Registry Number 62-56-6. This substance was identified in the categorization of the Domestic Substances List as a high priority for action under the Ministerial Challenge. Thiourea was identified as a high priority as it was considered to pose greatest potential for exposure (GPE) to individuals in Canada and had been classified by other agencies on the basis of carcinogenicity and reproductive/developmental toxicity. The substance did meet the ecological categorization criterion for persistence in water, soil and sediment but it did not meet the criterion for bioaccumulation potential or inherent toxicity to aquatic organisms. Therefore, the focus of this assessment of thiourea relates to human health risks.

According to information reported under section 71 of CEPA 1999, thiourea was imported into Canada in 2006 in a quantity ranging between 10 000 kg and 100 000 kg. Thiourea is used in metal finishing solutions and in etching treatments used for printed circuit boards, and as a reducing agent in the production of thiourea dioxide, a chemical intermediate, a reactant in the copper refinery industry and a rust inhibitor. In addition, thiourea may be included in silver polish, tarnish removers, metal cleaners, black and white photographic chemicals, blueprint papers and pharmaceutical synthesis.

Exposure to thiourea via the general environment is considered to be negligible; therefore, the predominant source of general population exposure to thiourea is expected to be as a result of its presence in consumer products.

Based principally on the weight of evidence based assessments of international or national agencies, a critical effect for the characterization of risk to human health for thiourea is carcinogenicity. The substance induced tumours at multiple sites in male and female rats and in the mammary gland in mice. Although thiourea appears to be only weakly genotoxic, the mode of induction of tumours has not been fully elucidated; therefore, it cannot be precluded that the tumours observed in experimental animals resulted from direct interaction with genetic material. In addition, the margins between upper-bounding estimates of exposure through inhalation and through dermal routes during use of consumer products containing thiourea and critical effect levels for non-cancer effects in short-term and reproductive toxicity studies may not be adequate to account for the uncertainties in the databases on exposure and effects, particularly in view of the uncertainties in the mode of induction of tumours.

On the basis of the carcinogenicity of thiourea, for which there may be a probability of harm at any level of exposure, as well as the potential inadequacy of the margins of exposure for non-cancer effects, it is concluded that thiourea is a substance that may be entering the environment in a quantity or concentration or under conditions that constitute or may constitute a danger in Canada to human life or health.

On the basis of ecological hazard and reported releases of thiourea, it is concluded that this substance is not entering the environment in a quantity or concentration or under

conditions that have or may have an immediate or long-term harmful effect on the environment or its biological diversity, or that constitute or may constitute a danger to the environment on which life depends. Although thiourea does meet criteria for persistence, it does not meet the criterion for bioaccumulation potential as set out in the *Persistence and Bioaccumulation Regulations.*

In addition and where relevant, research and monitoring will support verification of assumptions used during the screening assessment and, where appropriate, the performance of potential control measures identified during the risk management phase.

Based on the information available, thiourea meets one or more of the criteria set out in section 64 of CEPA 1999.

Introduction

The *Canadian Environmental Protection Act, 1999* (CEPA 1999) (Canada 1999) requires the Minister of the Environment and the Minister of Health to conduct screening assessments of substances that have met the categorization criteria set out in the Act to determine whether these substances present or may present a risk to the environment or human health. Based on the results of a screening assessment, the Ministers can propose to take no further action with respect to the substance, to add the substance to the Priority Substances List (PSL) for further assessment, or to recommend that the substance be added to the List of Toxic Substances in Schedule 1 of the Act and, where applicable, the implementation of virtual elimination.

Based on the information obtained through the categorization process, the Ministers identified a number of substances as high priorities for action. These include substances that

- met all of the ecological categorization criteria, including persistence (P), bioaccumulation potential (B) and inherently toxic to aquatic organisms, and were believed to be in commerce; and/or
- met the categorization criteria for greatest potential for exposure (GPE) or presented an intermediate potential for exposure (IPE), and had been identified as posing a high hazard to human health based on classifications by other national or international agencies for carcinogenicity, genotoxicity, developmental toxicity or reproductive toxicity.

The Ministers therefore published a notice of intent in the *Canada Gazette*, Part I, on December 9, 2006 (Canada 2006), which challenged industry and other interested stakeholders to submit, within specified timelines, specific information that may be used to inform risk assessment, and to develop and benchmark best practices for the risk management and product stewardship of those substances identified as high priorities.

The substance thiourea was identified as a high priority for assessment of human health risk because it was considered to present GPE and had been classified by other agencies on the basis of carcinogenicity, reproductive toxicity and developmental toxicity. The Challenge for thiourea was published in the *Canada Gazette* on May 12, 2007 (Canada 2007). A substance profile was released at the same time. The substance profile presented the technical information available prior to December 2005 that formed the basis for categorization of this substance. As a result of the Challenge, submissions of information were received.

Although thiourea was determined to be a high priority for assessment with respect to human health and it also met the ecological categorization criterion for persistence, it did not meet the criteria for potential for bioaccumulation and inherent toxicity for aquatic organisms. Therefore, this assessment focuses principally on information relevant to the evaluation of risks to human health.

Under CEPA 1999, screening assessments focus on information critical to determining whether a substance meets the criteria for defining a chemical as toxic as set out in section 64 of the Act, where

> "64. […] a substance is toxic if it is entering or may enter the environment in a quantity or concentration or under conditions that
>
> (*a*) have or may have an immediate or long-term harmful effect on the environment or its biological diversity;
>
> (*b*) constitute or may constitute a danger to the environment on which life depends; or
>
> (*c*) constitute or may constitute a danger in Canada to human life or health."

Screening assessments examine scientific information and develop conclusions by incorporating a weight of evidence approach and precaution.

This screening assessment includes consideration of information on chemical properties, hazards, uses and exposure, including the additional information submitted under the Challenge. Data relevant to the screening assessment of this substance were identified in original literature, review and assessment documents, stakeholder research reports and from recent literature searches, up to March 2008 for the human health exposure and effects sections of the document. Key studies were critically evaluated; modelling results may have been used to reach conclusions. Evaluation of risk to human health involves consideration of data relevant to estimation of exposure (non-occupational) of the general population, as well as information on health hazards (based principally on the weight of evidence assessments of other agencies that were used for prioritization of the substance). Decisions for human health are based on the nature of the critical effect and/or margins between conservative effect levels and estimates of exposure, taking into account confidence in the completeness of the identified databases on both exposure and effects, within a screening context. The screening assessment does not represent an exhaustive or critical review of all available data. Rather, it presents a summary of the critical information upon which the conclusion is based.

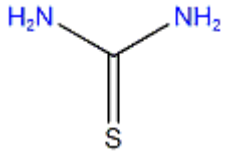
This screening assessment was prepared by staff in the Existing Substances Programs at Health Canada and Environment Canada and incorporates input from other programs within these departments. This assessment has undergone external written peer review/consultation. Comments on the technical portions relevant to human health were received from scientific experts selected and directed by Toxicology Excellence for Risk Assessment (TERA) including Michael Jayjock (The Lifeline Group), John Christopher (California Department of Toxic Substances Control) and Wendy Heiger-Bernays (Boston University School of Public Health & The Science Collaborative). While external comments were taken into consideration, the final content and outcome of the screening risk assessment remain the responsibility of Health Canada and Environment Canada. Additionally, the draft of this screening assessment was subject to a 60-day

public comment period. The critical information and considerations upon which the assessment is based are summarized below.

Substance Identity

For the purposes of this report, this substance will be referred to by its Domestic Substances List (DSL) inventory name, thiourea.

Table 1. Substance identity

Chemical Abstracts Service Registry Number (CAS RN)	62-56-6
Name on Domestic Substances List (DSL)	Thiourea
Other names	b-Thiopseudourea; 2-Thiourea; Isothiourea; NSC 5033; Pseudothiourea; Pseudourea (NH2.C(OH):NH), thio-; Pseudourea, 2-thio-; Thiocarbamide; THU; TsIZP 34; UN 2810; Urea, 2-thio; Urea, thio-
Chemical formula	CH_4N_2S
Chemical group (DSL stream)	Discrete organics
Chemical structure	
Simplified Molecular Input Line Entry System (SMILES)	C(=S)NN
Molecular mass	76.12 g/mol

Physical and Chemical Properties

A summary of the key physical and chemical properties of thiourea is presented in Table 2.

Table 2. Physical and chemical properties for thiourea

Property/Units	Type	Value[1]	Reference
Melting point (ºC)	Experimental	177	Sax 1984
		182	PhysProp 2003
Boiling point (ºC)		Decomposes	Verschueren 2001
	Modelled	157.8	MPBPWIN 2000
Vapour pressure (Pa) at 25ºC	Extrapolated	0.37 (2.8×10^{-3} mm Hg)	PhysProp 2003
	Estimated	2.44×10^{-2} (1.83×10^{-4} mm Hg)	CHEMFATE 2007
Henry's Law constant at 25ºC ($Pa \cdot m^3/mol$)	Experimental	1.31×10^{-5} (1.29×10^{-10} atm-m^3/mole)	Hine and Mookerjee 1975
Log K_{ow} (Octanol-water partition coefficient) (dimensionless)	Experimental	-1.02	Mackay et al. 2006
	Experimental	-0.95 to -2.38	Mackay et al. 2006
Water solubility at 13-25ºC (mg/L)	Measured	91 800–142 000	ISHOW 1992; Milleman and Ehrenberg 1982
Log K_{oc} (Organic carbon-water partition coefficient) (dimensionless)	Modelled	0.44	PCKOCWIN 2000

[1] If different, values in brackets represent the original ones as reported by the authors or as estimated by the models.

Sources

Thiourea can be industrially synthesized using two different procedures. The first procedure involves the fusion of ammonium thiocyanate by heating dry ammonium thiocyanate, followed by extraction with a concentrated solution of ammonium thiocyanate and subsequent crystallization (Lewis 2001; O'Neil et al. 2001). The more commonly used method consists of treating cyanamide with hydrogen sulphide (Lewis 2001; O'Neil et al. 2001).

Based on a survey conducted under section 71 of CEPA 1999, no Canadian companies reported manufacturing thiourea in a quantity greater than or equal to the 100 kg

threshold in 2006. However, results from the same survey and from voluntary data submitted by industry indicated that the total quantity of thiourea that was imported into Canada in 2006 ranged between 10 000 kg and 100 000 kg (Environment Canada 2007a).

Thiourea can be found naturally in Laburnum shrubs and as a metabolite of *Verticillium albo-atrum* and *Bortrylio cinera* (Verschueren 2001).

Uses

According to submissions made under section 71 of CEPA 1999, thiourea is used in metal finishing solutions and in etching treatments used for printed circuit boards (Environment Canada 2007a), as a reducing agent in the production of thiourea dioxide, and as a chemical intermediate (Environment Canada 2007a; NTP 2005; Raffaelli et al. 1997). Thiourea is used as a reactant in the copper refinery industry (NPRI 2005) and as an accelerant in rubber production (Univar 2007, Ash and Ash 1998). It is also a component of products used on surfaces at pulp and paper mills manufacturing paper and paperboard food packaging and is used as a cleaner and scale remover in food plants; however, since surfaces are rinsed, transfer of thiourea to food is not expected (as per email from the Food Packaging and Incidental Additives Sections, Health Products and Food Branch, Health Canada, dated 18Mar2008 unreferenced). In addition, thiourea may be used as a rust inhibitor (Hosein 2005), in silver polish, tarnish removers and metal cleaners (HPD 2005), in the production of flame retardant resins used in nylon (IPCS 2003; Calamari and Harper 1994), as an auxiliary agent in the textile industry (BUA 1998), as a photographic fixing agent and as an agent to remove stains from negatives (Lewis 2001; Verschueren 2001). It is used as an additive in slurry and emulsion explosives (BUA 1998), and has been used in ore leaching of gold and silver from minerals (Laursen 2002; Morrison 1983; IPCS 2003; Yen 1992).

Other potential uses of thiourea include as an auxiliary agent in diazo paper (blueprint papers) as well as other types of copy paper (IPCS 2003), as a liquefier in animal hide adhesives (BUA 1998; O'Neil et al. 2001), and is used in organic synthesis as an intermediate, in dyes, as an analytical reagent for bismuth and selenite ions for use in amino resins and as a vulcanization accelerator (Ash and Ash 1998; Lewis 2001; Verschueren 2001; Winter 2005). In addition, thiourea may be used as a dry cleaning agent, in boiler water treatment (NTP 2005), as a corrosion inhibitor, for use in surfactants, and in pharmaceutical synthesis (Ash and Ash 1998; Lewis 2001; Winter 2005).

Thiourea and its derivatives, with the exception of thioglycolic acid and its salts and esters, are currently listed on Health Canada's Cosmetic Ingredient "Hotlist," prohibiting its use in cosmetic ingredients. [The "Hotlist" states specific restrictions for thioglycolic acid and its salts] (Health Canada 2007). However, this chemical may be used elsewhere or was used historically as an antimicrobial agent, as a humectant in skin conditioning agents (Gottschalck and McEwen 2004), and in hair preparations (Lewis 2001; Winter 2005).

Thiourea may be used in insecticides (NTP 2005) and agrochemicals, and it is a mold inhibitor (Ash and Ash 1998; Lewis 2001); however, according to the Pest Management Regulatory Agency (PMRA) there are no pesticides registered in Canada containing this chemical as an active ingredient or as a formulant (PMRA 2007a, 2007b).

Releases to the Environment

According to the submissions made under section 71 of CEPA 1999, releases of thiourea from industry to air, water and soil are considered to be negligible; however, between 100 and 1000 kg of thiourea were reported as being transferred to an off-site waste management facility (Environment Canada 2007a). Waste products from processing are not likely to be a source of environmental exposure since they are incinerated, used by brick and cement industries or disposed of in authorized dumps, where the leachate is collected and reintroduced into the production process (IPCS 2003). In the United States, some waste thiourea is disposed of by injecting it into Class I underground injection wells (TRI 2005).

Under the National Pollutant Release Inventory (NPRI), thiourea has had no reportable on-site emissions since 1994, except in 2002, when 50 kg of thiourea were released to air as fugitive emissions (NPRI 2007). From 1999 to 2002 there was a reported increase in the quantity of thiourea, from 12 kg to 23.55 kg (NPRI 2007), being sent to off-site municipal sewage treatment plants prior to final disposal. Since 2002 there has been no reported off-site disposal of thiourea. Based on the physical and chemical properties and use pattern, if released to the environment, thiourea would be expected to be found mainly in water (IPCS 2003).

Environmental Fate

As indicated in Table 2, thiourea has a low to moderate vapour pressure (1.83×10^{-4} to 2.8×10^{-3} mm Hg) and a very high water solubility (91 800 to 142 000 mg/L), which suggests that this substance would be removed from the atmosphere by wet deposition processes. Based on the very low Henry's Law constant (1.31×10^{-5} Pa-m^3/mole) and the very low log K_{oc} (0.44), thiourea is expected to remain in water.

The results of Level III fugacity modelling (Table 3), reveal that thiourea is expected to partition predominantly to water and/or soil, depending on the compartment of release.

Table 3. Results of the Level III fugacity modelling (EQC v. 2.02) for thiourea

Substance released to	Fraction of substance partitioning to each medium (%)			
	Air	Water	Soil	Sediment
Air only (100%)	0.018	27.5	72.4	0.046
Water only (100%)	1.7×10^{-8}	99.8	6.8×10^{-5}	0.17
Soil only (100%)	4.3×10^{-6}	21.6	78.4	0.036

Persistence and Bioaccumulation Potential

Environmental Persistence

According to its physical and chemical properties (Table 2) and the empirical and modelled degradation data below (tables 4a and 4b), thiourea meets the persistence criteria in water, soil and sediment (half-lives in soil and water ≥ 182 days and half-life in sediment ≥ 365 days) as set out in the *Persistence and Bioaccumulation Regulations* (Canada 2000).

Table 4a. Empirical data for persistence of thiourea

Medium	Fate process	Degradation value	Endpoint/Units	Reference
Water	Biodegradation	2.6	Biodegradation, % BOD (14 day test)	MITI 1992
Water	Hydrolysis	54 750	Half-life, (days)	Ellington et al. 1988

Table 4b. Modelled data for persistence of thiourea

Medium	Fate process	Degradation value	Degradation endpoint	Reference
Air	Atm. oxidation	0.25	Half-life (days)	AOPWIN 2000
Air	Ozone reaction	Not reactive	Half-life (days)	AOPWIN 2000
Water	Biodegradation	15	Half-life (days)	BIOWIN 2000, ultimate survey
Water	Biodegradation	0.77	Probability	BIOWIN 2000; MITI 1992, non-linear probability
Water	Biodegradation	0.61	Probability	BIOWIN 2000; MITI 1992, linear probability
Water	Biodegradation	1	Probability	TOPKAT 2004
Water	Hydrolysis	n/a[1]	Half-life (days)	HYDROWIN 2000
Soil	Hydrolysis	≥ 182 days	Half-life (days)	Based on the modelled half-life in water[2]
Sediment	Hydrolysis	≥ 728 days	Half-life (days)	Based on the modelled half-life in water[2]

[1] A hydrolysis rate could not be estimated for this type of compound.
[2] Values were derived from the modelled half-life in water using the extrapolation factors of Boethling et al (1995): $t_{1/2\ water}$: $t_{1/2\ sediment}$ = 1:1:4

Potential for Bioaccumulation

Since few experimental data on the bioaccumulation factor (BAF) and the bioconcentration factor (BCF) of thiourea were available (Table 5a), a quantitative structure-activity relationship (QSAR)-based weight-of-evidence approach (Environment Canada 2007b) was also applied using the BAF and BCF models shown in Table 5b. The weight of evidence indicates that thiourea does not meet the bioaccumulation criteria (BCF/BAF ≥ 5 000) as set out in the *Persistence and Bioaccumulation Regulations* (Canada 2000).

Table 5a. Empirical data for the bioaccumulation of thiourea

Test organism	Endpoint	Value (L/kg, wet weight)	Reference
Fish (carp)	Bioconcentration factor (BCF)	2.0	MITI 1992
Fish (carp)	BCF	0.2	MITI 1992

Table 5b. Modelled data for bioaccumulation of thiourea

Test organism	Endpoint	Value (L/kg, wet weight)	Reference
Fish	Bioaccumulation factor (BAF)	0.93	Arnot and Gobas 2003
Fish	Bioconcentration factor (BCF)	9.12	Arnot and Gobas 2003
Fish	BCF	3.16	OASIS Forecast 2005
Fish	BCF	0.95	BCFWIN 2000

Potential to Cause Ecological Harm

Thiourea meets the criterion for persistence in water, soil and sediment, but it does not meet the criterion for bioaccumulation potential as set out in the *Persistence and Bioaccumulation Regulations* (Canada 2000).

Experimental ecotoxicological data (ECOTOX database) (ECOTOX, 2006) indicate that thiourea does not cause significant harm to aquatic organisms at low concentrations. Experimental acute toxicity values vary within a range of 4.8–600 mg/L for algae and fish.

According to the submissions made under section 71 of CEPA 1999 (Environment Canada 2007a), releases of thiourea from industry to air, water and soil are considered to be negligible, although between 100 and 1000 kg of thiourea were reported as being transferred to an off-site waste management facility. However, since 2002 there has been no reported off-site disposal of thiourea under the National Pollutant Release Inventory (NPRI 2007). Given the quantity and nature of the releases, they are deemed unlikely to result in significant exposure of organisms in the environment.

Available information indicates that it is unlikely that thiourea is causing ecological harm in Canada.

Potential to Cause Harm to Human Health

Exposure Assessment

Measured concentrations upon which to base upper-bounding estimates of intake of thiourea were not available for any environmental media in Canada or elsewhere. Only one study was identified in which six seawater and six sediment samples were analyzed for thiourea in Japan in 1977 (IPCS 2003). Thiourea was not detected in seawater (detection limit of 0.011–0.4 mg/L) or in sediment (detection limit of 0.055 - 1 mg/kg) (Japan 2004; BUA 1998). This study was not deemed suitable to estimate upper-bounding intakes because the samples were taken from seawater and are older. It was not possible to estimate upper-bounding exposures to thiourea from the environment, given the limitations of the available information. However, according to the results of the section 71 notice CEPA 1999 (Environment Canada 2007a) and the National Pollutant Release Inventory (NPRI 2007), releases to air, water and soil are considered to be negligible.

There is potential for the general population in Canada to be exposed to thiourea through the use of consumer products such as silver polish, metal cleaners, black-and-white photographic toning solution, textiles, diazo(blueprint) paper and various other copy papers. Sufficient information was only available to derive estimates for inhalation and dermal exposures to thiourea through the use of silver polish/metal cleaners and the use of black-and-white photographic toning solution (Appendix 1).

The ConsExpo evaporation model (RIVM 2006a) was used to predict air concentrations of thiourea from the use of metal cleaner and photographic toning solution by assuming that not all of the substance will be released from the product during use. This resulted in an acute dose of 0.002 mg/kg bw per day for metal cleaner and 0.001 mg/kg bw per day for photographic toning solution. Ackermann and Flynn (1987) derived a dermal permeability coefficient (Kp) for thiourea (9.6×10^{-5} cm/hr) using nude mouse skin. This value was very similar to the Kp value estimated by DERMWIN (2000), which takes into account the octanol-water partition coefficient. Taking the Ackermann and Flynn (1987) Kp value into consideration, the single event doses resulting from dermal exposure to

metal cleaner and photographic toning solution were estimated to be 0.02 and 0.1 mg/kg-bw per day for the two uses respectively.

Confidence in the exposure database is considered to be low, as no data were available on concentrations of thiourea in environmental media or in food in Canada or elsewhere. However, based on available information, industrial releases to the environment are considered to be negligible. There is also low confidence in the estimate of exposure from consumer products. According to the results from the section 71 notice of CEPA 1999, the reported uses of thiourea were mainly for industrial purposes, which are unlikely to lead to exposure of the general population. However, based on information obtained from other sources, thiourea may be found in various consumer products; although lack of data on concentrations of thiourea in these products, as well as the frequency and quantities of their use in Canada preclude derivation of more accurate estimates of exposure levels for the general population.

Health Effects Assessment

An overview of the toxicological database is presented in Appendix 2.

Thiourea has been classified by the National Toxicology Program (NTP) as "reasonably anticipated to be a human carcinogen" (NTP 2005) and by the European Community as a Category 3 Carcinogen ("Causes concern for humans owing to possible carcinogenic effects") (European Commission 1998a; ESIS 2006). These classifications were based on observed thyroid adenomas and carcinomas in male and female rats administered 0.25% thiourea in drinking water (350 mg/kg bw/day) for up to 24 months (Purves and Griesbach 1947). Squamous cell carcinomas of the zymbal gland and meibomian glands observed in male rats exposed to 0.2% (280 mg/kg bw/day) thiourea in drinking water or intraperitoneal injection followed by 0.2% in drinking water for up to 23 months (Rosin and Ungar 1957; Ungar and Rosin 1960). Administration of thiourea to rats in the diet of 5 mg/kg bw/day for 24 months induced hepatocellular adenomas (Fitzhugh and Nelson 1948). In addition, an increase in mammary tumours was reported in female mice exposed to thiourea (0.1–0.2% or 140–280 mg/kg bw/day) in the drinking water for up to six months (Vasquez-Lopez 1949). It is noted that the NTP assessment is based on the International Agency for Research on Cancer (IARC) 1974 evaluation of thiourea with a conclusion of *sufficient evidence of carcinogenicity in experimental animals*. In the more recent evaluation, IARC concluded that thiourea was not classifiable as to its carcinogenicity (Group 3) based on inadequate evidence in humans and limited evidence in experimental animals (IARC 2001). No adequate human studies have been reported on the potential relationship between exposure to thiourea and cancer in humans (IARC 2001; IPCS 2003; NTP 2005).

Thiourea has not been extensively tested for genotoxicity *in vivo.* Studies in *Drosophila* have yielded mixed results. Review of the genotoxicity data *in vitro* shows that thiourea is not mutagentic in bacteria but produces mixed results in mammalian cells with consistently positive results for cell transformation and induction of chromosomal recombination in yeast (IARC 2001; IPCS 2003).

Although mode of action analyses are beyond the scope of this screening level assessment, the IPCS (2003) has suggested that thiourea is not considered to be a genotoxic carcinogen and that the development of thiourea-induced thyroid tumours may involve inhibition of peroxidase in the thyroid gland, leading to decreased thyroid hormone production and increased proliferation as a result of an increase in the secretion of thyroid-stimulating hormone. However, a definitive conclusion regarding mode of action for carcinogenicity could not be made (IARC 2001, IPCS 2003) and, in view of the mixed results from the genotoxicity assays, the possible contribution of interaction with genetic material to tumour induction cannot be precluded.

The critical non-neoplastic effects occur in the thyroid. The lowest-observed-adverse-effect level identified was 27.5 mg/kg bw/day in rats exposed orally for up to three years, based on enlargement of the thyroid gland and reduced body weight gain (Hartzell 1942, 1945). Thyroid effects were also observed in subchronic studies in male lambs (Sokkar et al. 2000) and female lambs (Nasseri and Prassad 1987a) at 50 mg/kg bw/day, including thyroid gland hyperplasia in males and enlargement of the thyroid gland and a significant decrease in serum T4 in females. A reduction of iodine levels in the thyroid was reported in rats orally administered 70 mg/kg bw/day thiourea for 10 days (Astwood et al. 1945).

The European Commission has also classified thiourea as a Reproductive Category 3 based on "p*ossible risk of harm to the unborn child"* (European Commission, 1998a; European Commission, 1998b; ESIS, 2006).

Developmental effects observed in young lambs orally administered thiourea include hypothyroidism, reduction of testosterone levels, small and empty seminiferous tubules and "ill developed testes" in males and infantile and stunted external genitalia and an absence of estrus and retarded mammary development in females at 50 mg/kg bw/day (Sokkar et al., 2000; Nasseri and Prassad, 1987b). In addition, effects on reproductive organs observed in female lambs following subchronic oral administration include non-significantly reduced size and weight of ovaries, uterine horn and vagina (Alavi Shoushtari & Safaii 1993). Oral administration of greater than 35 mg/kg bw/day thiourea to male rats produced a reduction or cessation of spermatogenesis (Fitzhugh & Nelson 1948). IPCS (2003) suggested that the effects on reproductive organs in developing animals are related to inhibition of thyroid function.

Individual cases of contact dermatitis following exposure to thiourea from the use of diazo copy paper and other types of copy paper and silver polish have been reported, with some cases being sensitive to UV light (see Appendix 2). Thiourea derivatives used as accelerators in the rubber industry have also been shown to induce allergic contact dermatitis.

Confidence in the toxicity dataset is considered to be low to moderate. Data are available for acute toxicity, repeat dose toxicity, genetic toxicity, reproductive toxicity, developmental toxicity, chronic toxicity and carcinogenicity; however, there is a paucity

of *in vivo* genotoxicity assays, and many of the carcinogenicity studies are dated and do not meet current testing standards.

Characterization of Risk to Human Health

Based principally on the weight of evidence based assessments or classifications of several international or national agencies (IARC, IPCS, EC and NTP), a critical effect for characterization of risk to human health for thiourea is carcinogenicity. The substance induced tumours at multiple sites in male and female rats and in the mammary gland in mice. As thiourea appears to be only weakly genotoxic, IPCS (2003) has postulated that the substance is not a genotoxic carcinogen. However, the modes of action for induction of the various tumour types observed in exposed rats and mice have not been fully elucidated, and such analyses are beyond the scope of this Challenge screening assessment. Therefore, a mode of induction involving direct interaction with genetic material cannot be precluded.

Data were insufficient to quantify exposure from the general environment, although it is expected to be negligible; therefore, to characterize the risk for non-cancer effects, the estimated inhalation and dermal exposures (combined) from consumer products during the use of metal cleaners (0.023 mg/kg bw per day) and photographic toning solutions (0.11 mg/kg bw per day), were compared to the lowest short-term oral toxicity values (lowest-observed-effect level [LOEL] 70 mg/kg bw/day). The resulting margin of exposure (MOE) for silver polish is approximately 3000, while that for photographic toning solution is approximately 600. These margins for consumer product exposure scenarios, although conservative in nature, may not be adequate to account for uncertainties in the databases on exposure and effects, particularly in view of the uncertainties regarding the mode(s) of action for the induction of tumours as well as the steepness of the relationship between toxicity and duration of exposure (i.e., LOELs for short-term, subchronic and chronic exposure were 70, 50 and 27.5 mg/kg bw per day, respectively).

Uncertainties in Evaluation of Risk to Human Health

The scope of this Challenge screening assessment does not take into account possible differences between humans and experimental species in sensitivity to effects induced by the substance, particularly in light of the lack of adequate epidemiological investigations. The available genotoxicity studies do not provide a clear understanding of the potential of thiourea to induce genetic damage. Additionally, the mode(s) of induction of tumours observed in rodents have not been fully elucidated, although a non-genotoxic mode of action has been postulated for the thyroid tumours. There are uncertainties in the quantification of exposure-response, as the majority of toxicological data are quite old; however, the reported effect levels are generally in the same range. In addition, repeated dose studies are available from administration via the oral route only. Information from studies conducted via inhalation or dermal administration would add to the confidence in the database.

Data were inadequate to permit quantification of exposure to thiourea from environmental media in Canada; however, the available information on releases in Canada indicates that concentrations in these media are likely negligible. Estimates of exposure from the use of consumer products containing thiourea were based on conservative assumptions and may overestimate actual exposure; however, data currently available are insufficient to derive quantitative estimates of the potential contribution of other consumer products to the exposure of the general population in Canada to thiourea.

Conclusion

Based on the available information, it is concluded that thiourea is not entering the environment in a quantity or concentration or under conditions that have or may have an immediate or long-term harmful effect on the environment or its biological diversity, or that constitute or may constitute a danger to the environment on which life depends. Additionally, thiourea meets the criterion for persistence, but it does not meet the criterion for bioaccumulation potential as set out in the *Persistence and Bioaccumulation Regulations.*

On the basis of carcinogenicity of thiourea, for which there may be a probability of harm at any level of exposure, as well as the potential inadequacy of the margins of exposure for non-cancer effects, it is concluded that thiourea is a substance that may be entering the environment in a quantity or concentration or under conditions that constitute or may constitute a danger in Canada to human life or health.

It is therefore concluded that thiourea does not meet the criteria in paragraphs 64(a) and 64(b) of CEPA 1999, but it does meet the criterion in paragraph 64(c) of CEPA 1999.

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Appendix 1. Upper-Bounding Estimates of Exposure to Thiourea from Consumer Products

Consumer product[1]	Assumptions	Estimated exposure
Silver polish	**Inhalation (evaporation)** - Use ConsExpo model version 4.1, exposure to vapour, evaporation as mode of release, area of release increases over time (RIVM 2006a). - Based on a reported maximum concentration of 7% found in various silver and metal cleaners (HPD 2005; Laursen 2002). - Assume amount of product used is 10 g/event, a room volume of 15 m^3, exposure duration of 60 minutes, release area of 1.71 m^2 (for metal countertop), use Langmuir's method for mass transfer rate (RIVM 2006b), application duration of 60 minutes, molecular weight matrix of 19.35 g/mol (18 g/mol/0.93). - Assume ventilation rate of 1 time/hr. - Assume 100% uptake. - Assume adult exposed weighs 70.9 kg and breathes 16.2 m^3 of air per day (Health Canada 1998). - Assumes one event per day.	Mean event concentration = 0.204 mg/m^3 Acute dose = 0.0019 mg/kg bw per day
Silver polish	**Dermal[2]** - Based on a reported maximum concentration of 7% in various silver and metal cleaners (HPD 2005, Laursen 2002).and density of product to be 1.049 g/cm^3 (Gaudrault 2007); the concentration of thiourea in silver polish is 73.4 mg/cm^3. - Assume a Kp value (permeability coefficient) of 9.6 x 10^{-5} cm/hr (Ackermann and Flynn 1987) (estimated value from DERMWIN [2000] is 1.12 x 10^{-4} cm/hr). - Assume an exposed surface area of 215 cm^2, exposure duration of 1 hr (RIVM 2006b). - Assume adult exposed weighs 70.9 kg (Health Canada 1998). - Assumes one event per day. Estimated dose per event = $\frac{Kp \times C \times ET \times SA}{BW}$ = (9.6 x 10^{-5} cm/hr)(73.4 mg/cm^3)(1 hr)(215 cm^2)/70.9 kg = 0.021 mg/kg bw per day	Estimated dose = 0.021 mg/kg bw per day
Photo finishing (B+W photo; sepia toner)	**Inhalation (evaporation)** - Use ConsExpo model version 4.1, exposure to vapour, evaporation as mode of release, area of release increases over time (RIVM 2006a). - Based on a reported maximum concentration of 5% found in toning solution (Photographers' Formulary, Inc. 2006), assume density of water is 1 g/cm^3. - Technical data sheet states that 5 g of thiourea is placed in 100 mL of water (applied amount is approximately 105 g) (Photographers' Formulary, Inc. 2006). - Assume a room volume of 9 m^3, exposure duration of 8 hours, and ventilation rate of 0.5 time/hr (US EPA 1986). - Assume release area is 1 m^2, molecular weight matrix is 18.9 (18 g/mol/0.95), use Langmuir's method for mass transfer rate, 100% uptake (RIVM 2006b). - Assume 100% uptake. - Assume adult exposed weighs 70.9 kg and breathes 16.2 m^3 of air per day (Health Canada 1998). - Assume one event per day	Mean event concentration = 0.144 mg/m^3 Acute dose = 0.0014 mg/kg bw per day

Photo finishing (B+W photo; sepia toner)	**Dermal** - Based on a reported maximum concentration of 5% found in toning solution (Photographers' Formulary, Inc. 2006), assume the density of the product to be 1 g/cm^3 (density of water); the concentration is 50 mg/cm^3. - Assume a Kp value (permeability coefficient) of 9.6 x 10^{-5} cm/hr (Ackermann and Flynn 1987) (value estimated from DERMWIN [2000] is 1.12 x 10^{-4} cm/hr). - Assume an exposed surface area of 200 cm^2, exposure duration of 8 hrs (US EPA 1986). - Assume adult exposed weighs 70.9 kg (Health Canada 1998). - Assume one event per day Estimated dose per event = $\frac{Kp \times C \times ET \times SA}{BW}$ = (9.6 x 10^{-5} cm/hr)(50 mg/cm^3)(8 hrs)(200 cm^2)/70.9 kg = 0.108 mg/kg bw per event	Acute dose = 0.11 mg/kg bw per day

[1] Since these products are used primarily by adults (20–59 years old), estimated exposures have been derived for this age group only.
[2] Dermal scenarios were also run using the ConsExpo model version 4.1. Similar results to those presented above were obtained.

Appendix 2. Summary of Health Effects Information for Thiourea

Endpoint	Lowest effect levels/results
Acute toxicity	**Lowest oral LD_{50}** (rat) = 125 mg/kg bw (Dieke et al. 1947) **Lowest inhalation LC_{50}** (rats) > 195 mg/m^3 (TNO 1979a) **Lowest dermal LD_{50}** (rabbits) > 2500 mg/kg bw (TNO 1978)
Short-term repeated dose toxicity	**Lowest oral LOEL** (rat) = 70 mg/kg bw/day based on reduction of iodine level in the thyroid gland following 10 days of exposure (Astwood et al. 1945) (N.B.: A slight increase in thyroid weight was observed in rats administered a lower dose [i.e., 25 mg/kg bw/day]; however, no statistical analyses were presented. [MacKenzie and MacKenzie 1943]) (Additional studies: Astwood 1943; Smith 1950; Keston et al. 1944; MAK 1988; Jones 1946; Malcom et al. 1949) **Inhalation** No studies identified
Subchronic toxicity	**Lowest oral LOEL** (lambs) = 50 mg/kg bw/day based on significantly reduced body weight, significant reduction in erythrocyte and leukocyte numbers and T3 and testosterone levels, ill-developed testes and small empty seminiferous tubules following daily administration for 3.5 months (Sokkar et al. 2000) (Additional studies: Morris et al. 1946; Malcolm et al. 1949; Hazelton 1987; Nasseri and Prassad 1987a; Sokkar et al. 2000) **Inhalation** No studies identified.
Chronic toxicity/carcinogenicity	**Oral carcinogenicity bioassays in rats** Rats were administered 0.25% (350 mg/kg bw/day) thiourea in drinking water for 12–24 months. Thyroid follicular-cell tumours were observed in 8/10 male New Zealand albino rats (4/10 thyroid carcinomas) and 8/10 female New Zealand albino rats (3/10 thyroid carcinoma) and 6/10 male Wistar rats (0/10 thyroid carcinomas). (Purves and Griesbach 1947). (N.B.: No control group was used in this study.) In rats administered 0 or 0.2% in drinking water for up to 26 months an increase in epidermoid carcinomas of the external auditory duct or meibomian glands was observed in 17/19 albino rats versus 0/12 in controls (Rosin and Ungar 1957). In rats administered 0.2% thiourea in drinking water, squamous cell carcinomas of the Zymbal gland and/or meibomian gland appeared in all but one treated animal (Ungar and Rosin 1960) (N.B. In Ungar and Rosin 1960 the rats used were survivors of tumour transplantation studies in which the intrascapular implant was considered to have failed.) Albino rats (male and female) were administered 0, 0.01, 0.025, 0.05, 0.1, 0.25, 0.5 or 1% thiourea in the diet (0, 5, 12, 25, 50, 125, 250, 500 mg/kg bw/day) for

Endpoint	Lowest effect levels/results
	24 months. Moderate to marked thyroid hyperplasia and enlargement of the thyroid gland was observed at 0.25%–1% (125–500 mg/kg bw/day). There was an increased incidence of liver tumours (hepatic cell adenomas) at 5 mg/kg bw/day and higher (3/5, 4/8, 2/8 and 5/8 at 5 mg/kg bw/day, respectively). All animals in the two highest dose groups died before 17months. (Fitzhugh and Nelson 1948; Deichmann et al. 1967) In female mice (R3) administered 0.1–0.2% (140–280 mg/kg bw/day) thiourea in drinking water for 4 to 6 months, mammary tumours observed in 54% of exposed mice (dose not specified in secondary source) versus 28% in controls (Vasquez-Lopez 1949). **Lowest oral LOAEL** (rat) = 27.5 mg/kg bw/day based on enlarged thyroid gland and reduction in body weight gain in rats exposed to thiourea daily in drinking water for 2 years (Hartzell 1942, 1945) **Inhalation** No studies identified (Additional studies: Fitzhugh and Nelson 1948; Gorbman 1947; Dalton et al. 1948; Casas and Koppisch 1952; Gargus et al. 1969; Purves and Griesbach 1947; Rosin and Rachmilewitz 1954; Rosin and Ungar 1957; Ungar and Rosin 1960; Randomski et al. 1965; Deichmann et al. 1967; Hartzell 1942, 1945; Hazelton 1987; Morris et al. 1946)
Developmental toxicity	**Lowest oral LOEL** (lambs) = 50 mg/kg bw/day based on thyroid gland hyperplasia, significantly reduced body weight, reduction of erythrocytes, leukocytes, T3 and testosterone levels, small empty seminiferous tubules and "ill developed testes" in young male lambs exposed for 3.5 months (Sokkar et al. 2000) and based on infantile and stunted external genitalia and lack of estrus and retarded mammary development in young female lambs exposed for up to 6 months (Nasseri and Prassad 1987b) (Additional studies: Sokkar et al 2000; Teramoto et al. 1981; Ruddick et al. 1976; Kern et al. 1980; Nasseri and Prassad 1987b)
Reproductive toxicity	Lowest **oral LOEL** (lambs) = Female lambs administered 50 mg/kg bw/day thiourea orally for 80 days revealed a slight but not statistically significant decrease in size and weight of the ovaries, uterine horn and vagina. Histological exam showed atretic follics of the ovaries and shorter endometrial cells. (Alavi Shoushtari and Safaii 1993) (Additional studies: Rat administered thiourea in diet exhibited a reduction in or cessation of spermatogenesis reported by IPCS 2003 at doses greater than 35 mg/kg bw/day following 24 months exposure [Fitzhugh and Nelson 1948])

Genotoxicity and related endpoints: *in vitro*				
Endpoint	**Results and references**			
Gene mutation	**Species, strain**	**Result**	**Metabolic activation**	**Reference**
	Salmonella typhimurium TA 97	Negative	+/-	Brams et al. 1987 Zeiger et al. 1988
	Salmonella typhimurium TA 98	Negative	+/-	Simmon 1979a Dunkel et al. 1984 Brams et al. 1987

			Zeiger et al. 1988
Salmonella typhimurium TA 100	Negative	+/-	Simmon 1979a Yamaguchi 1980 Dunkel et al. 1984 Brams et al. 1987 Zeiger et al. 1988
Salmonella typhimurium TA1535	Negative	+/-	Simmon 1979a Rozenkranz and Poirier 1979 Dunkel et al. 1984 Zeiger et al. 1988
Salmonella typhimurium TA1535/pSK1002 umu test	Negative	+/-	Nakamura et al. 1987
Salmonella typhimurium TA1537	Negative	+/-	Simmon 1979a Dunkel et al. 1984
Salmonella typhimurium TA1538	Negative	+/-	Rozenkranz and Poirier 1979 Simmon 1979a Dunkel et al. 1984
Escherichia coli SOS repair	Negative	+/-	Brams et al. 1987 Kevekordes et al. 1999
Escherichia coli WP2 *uvr*A	Negative	+/-	Dunkel et al. 1984
Escherichia coli pol A	Negative	+	Rosenkranz and Poirier 1979 McCarroll et al. 1981
		-	McCarroll et al. 1981
Escherichia coli uvr/rec strains	Positive	-	Hellmér and Bolcsfoldi 1992
	Negative	+	Hellmér and Bolcsfoldi 1992
Escherichia coli K12	Negative	+	Mamber et al. 1984
	Not tested	-	Mamber et al. 1984
Escherichia coli RK	Negative	+/-	Hayes et al. 1984
Aspergillus nidulans	Negative	-	Crebelli et al. 1986
Saccharamyces cerevisiae	Positive	-	Schiestl 1989 Schiestl et al. 1989 Galli and Schiestl 1995, 1996, 1998
		+	Galli and Schiestl 1998 Egilsson et al. 1979 Wilkie and Gooneskera 1980
Saccharamyces cerevisiae trp locus	Positive	+	Morita et al. 1989
	Negative	-	Morita et al. 1989
Saccharamyces cerevisiae D7 trp locus	Positive	Not indicated	Jiang et al. 1989
Drosophila melanogaster	Positive	-	Batiste-Alentorn et al. 1991
	Weakly positive	-	Vogel & Nivard 1993
	Inconclusive	-	Batiste-Alentorn et al. 1994, 1995

		Negative	-	Rodriguez-Arnaiz 1997
	Mouse L5178Y cells	Weakly positive	+	Myhr and Caspary 1988 Wangenheim and Bolcsfoldi 1988
			-	Wangenheim and Bolcsfoldi 1988
		Negative	+	Mitchell et al. 1988
			-	Mitchell et al. 1988 Myhr and Caspary 1988
	Chinese hamster ovary cells (V79), *hprt* locus	Negative	-	Bradley et al. 1982
		Positive	+/-	Ziegler-Skylakakis et al. 1985
	Chinese hamster ovary cells (V79), cell sub-line Sp5	Negative	-	Helleday et al. 1998
Sister chromatid exchange	**Negative** Chinese hamster V79 cells (-activation) (Bradley et al. 1982)			
Unscheduled DNA synthesis	**Weakly positive** Rat liver cells (Ziegler-Skylakakis et al. 1985) **Negative** Rat liver cells (-activation, + activation not tested) (Lonati-Galligani et al. 1983; Fautz et al. 1991)			
Mitotic recombination	**Negative** *Saccharamyces cerevisiae* D3 (+/- activation) (Simmon 1979b)			
Recombination	**Positive** Transformed human lymphoblastoid GM6804 cells (Aubrecht et al. 1995)			
Micronucleus formation	**Positive** Syrian hamster embryo cells (- activation, + not tested) (Fritzenschaf et al. 1993) **Weakly positive** Chinese hamster V79 (Ziegler-Skylakakis et al. 1998)			
DNA strand breaks	**Positive** Rat hepatocytes *in vitro* (-activation, not tested + activation) (Sina et al. 1983) **Negative** Rat hepatocytes *in vitro* (-activation, not tested + activation) (Fautz et al. 1991)			
Cell transformation	**Positive** Syrian hamster embryo cells (-activation, + not tested) (Pienta et al. 1977) Rauscher virus-infected rat embryo cells (-activation, + not tested) (Dunkel et al. 1981) **Weakly positive** Bovine papilloma virus DNA-enhanced C3H10T1/2 cells (-activation, + not tested) (Kowalski et al. 2000)			
DNA synthesis inhibition	**Positive** Human fibroblast cells (Painter 1977)			
Genotoxicity and related endpoints: *in vivo*				
Endpoint	**Results and reference**			
Gene mutation	**Positive** *Drosophila melanogaster* (Batiste-Alentorn et al. 1991) **Weakly Positive** *Drosophila melanogaster* (Vogel and Nivard 1993) **Negative** *Drosophila melanogaster* (Rodriguez-Arnaiz 1997) **Inconclusive** *Drosophila melanogaster* (Batiste-Alentorn et al. 1994, 1995)			
Micronucleus test	**Negative** Rats treated with two successive oral doses within 24 hours (TNO 1979b)			
Effects in Humans				

Case Studies	Individual cases of contact dermatitis following exposure to thiourea from the use of diazo copy paper and most other types of copy paper were reported (Van der Leun et al 1977; Nurse 1980; Kellett et al. 1984, Liden 1984; Dooms-Goossens et al. 1987; Niinimaki 1989; Pashe-Koo and Grosshans 1991; Torres et al. 1992; Geier and Fuchs 1993; Bartels and Schauder 1994; van Gerwen et al. 1996; Kanerva et al. 2000). Contact dermatitis has been reported from thiourea in silver polish Dooms-Goosenens et al. 1988) Thiourea derivatives used as accelerators in the rubber industry have been shown to produce allergic contact dermatitis (Kanerva et al. 1994; McCleskey and Swerlick 2001).