Government of Canada / Gouvernement du Canada

# RISK MANAGEMENT APPROACH for

# Benzene, 1-chloro-2-[2,2-dichloro-1-(4-chlorophenyl)ethyl]- (Mitotane)

## Chemical Abstracts Service Registry Number (CAS RN): 53-19-0

Environment and Climate Change Canada
Health Canada

October 2017

Canada

# Summary of Proposed Risk Management

This document outlines the proposed risk management action for mitotane. In this case, based on the unique use of mitotane, the Government of Canada is considering implementing the significant new activity (SNAc) provisions under the *Canadian Environmental Protection Act, 1999* (CEPA). No risk management actions are being proposed to limit the essential use of mitotane as a therapeutic drug.

To inform the definition of 'significant new activities', information on the following items should be provided by December 27, 2017 to the contact details identified in section 8 of this document:

- Any manufacturing of mitotane or of mitotane-containing products in Canada (since 2006);
- Any imports of mitotane into Canada (since 2006), other than quantities previously reported during the public comment period on the Risk Management Scope document published on July 6th, 2013; and
- Any other use details in Canada (since 2006), beyond what is presented herein.

**Note:** The above summary is an abridged list of the action proposed to manage mitotane and of information sought to inform the risk management decision-making process. Refer to section 3 of this document for more complete details in this regard. It should be noted that the identified risk management action may evolve through consideration of additional information obtained from the public comment period, from other sources, and from the information presented in this document.

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# 1. Context

The *Canadian Environmental Protection Act, 1999* CEPA (Canada 1999) provides the authority for the Minister of the Environment and the Minister of Health (the ministers) to conduct assessments to determine if substances are toxic[1] to the environment and/or harmful to human health[2], and if so, to manage the associated risks.

In December 2006, 193 chemical substances were identified as high priorities for assessment due to their hazardous properties and their potential to pose risks to human health and the environment. In February 2007, as part of the Challenge under the Chemicals Management Plan, the ministers began publishing, for industry and stakeholder comments, profiles of batches containing 12 to 19 high-priority substances. New batches were released for comments every three months, and the information-gathering authority in section 71 of CEPA was used to collect specific information on these substances, where required.

The substance benzene, 1-chloro-2-[2,2-dichloro-1-(4-chlorophenyl)ethyl]-, Chemical Abstracts Service Registry Number (CAS RN)[3] 53-19-0, referred to throughout this document as “mitotane”, is included in Batch 12 of the Challenge.

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[1] Section 64 of CEPA: *For the purposes of* [Parts 5 and 6 of CEPA]*, except where the expression “inherently toxic” appears, 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.*

[2] A determination of whether one or more of the criteria of section 64 are met is based upon an assessment of potential risks to the environment and/or to human health associated with exposures in the general environment. For humans, this includes, but is not limited to, exposures from ambient and indoor air, drinking water, foodstuffs and the use of consumer products. A conclusion under CEPA on the substances in the Chemicals Management Plan is not relevant to, nor does it preclude, an assessment against the hazard criteria specified in the *Hazardous Products Regulations* and the *Controlled Products Regulations*, which are part of the regulatory framework for the Workplace Hazardous Materials Information System for products intended for workplace use. Similarly, a conclusion based on the criteria contained in section 64 of CEPA does not preclude actions being taken under other sections of CEPA or other Acts.

[3] [CAS RN] Chemical Abstracts Service Registry Number. The Chemical Abstracts Service information is the property of the American Chemical Society and any use or redistribution, except as required in supporting regulatory requirements and/or for reports to the Government of Canada when the information and the reports are required by law or administrative policy, is not permitted without the prior, written permission of the American Chemical Society.

# 2. Issue

## 2.1 Final Screening Assessment conclusion

Health Canada and Environment and Climate Change Canada conducted a joint scientific assessment relevant to the evaluation of mitotane in Canada. A notice summarizing the scientific considerations of the final screening assessment for mitotane was published in the *Canada Gazette*, Part I, on October 27, 2017 (Canada 2017a,b).

Based on the information available, the final screening assessment concludes that mitotane is toxic under paragraph 64*(a)* of CEPA because it is or may enter 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 (Canada 2017a,b).

Mitotane was also found to meet the criteria for persistence and bioaccumulation, as defined in the *Persistence and Bioaccumulation Regulations* made under CEPA (Canada 2000, 2017a,b).

However, mitotane does not meet the criteria in paragraphs 64*(b)* and *(c)* of CEPA, as it is not entering the environment in a quantity or concentration or under conditions that constitute or may constitute a danger to the environment on which life depends or a danger in Canada to human life or health.

For further information on the screening assessment conclusion for mitotane, refer to the final screening assessment, available from http://www.chemicalsubstanceschimiques.gc.ca/challenge-defi/batch-lot-12/index-eng.php.

## 2.2 Recommendation under CEPA

Based on the findings of the final screening assessment for mitotane conducted as per CEPA, the ministers recommend adding mitotane to the List of Toxic Substances in Schedule 1 of the Act[4].

Under certain circumstances, the ministers must make a specific proposal to recommend addition to the List of Toxic Substances and, where applicable, also

[4] When a substance is found to meet one or more of the criteria under section 64 of CEPA, the Ministers can propose to take no further action with respect to the substances, add the substances to the Priority Substances List (PSL) for further assessment, or recommend the addition of the substances to the List of Toxic Substances in Schedule 1 of the Act.

recommend the implementation of virtual elimination[5]. In this case, mitotane is found to meet the criteria for virtual elimination set out in paragraph 77(4) of CEPA.

## 2.3 Public comment period on the risk management scope

The Risk Management Scope document for mitotane, which summarized the proposed risk management action under consideration at that time, was published on July 6th, 2013. Industry and other interested stakeholders were invited to submit comments on the Risk Management Scope document during a 60-day comment period. Comments received on the Risk Management Scope document were taken into consideration in the development of this document. A summary of responses to public comments received is available from http://www.chemicalsubstanceschimiques.gc.ca/challenge-defi/batch-lot-12/index-eng.php.

# 3. Proposed risk management

## 3.1 Proposed environmental objective

Proposed environmental objectives are quantitative or qualitative statements of what should be achieved to address environmental concerns. In the case of toxic substances that result predominantly from human activity and that are persistent and bioaccumulative, the proposed environmental objective is usually the virtual elimination of the release of these substances into the environment.[6]. The proposed environmental objective will focus on limiting the introduction of mitotane to the environment to the greatest extent possible given the use of this substance as a chemotherapeutic drug.

## 3.2 Proposed risk management objective

Proposed risk management objectives set quantitative or qualitative targets to be achieved by the implementation of risk management regulations, instrument(s) and/or tool(s) for a given substance or substances. Based on the unique use of mitotane as a therapeutic drug and the socio-economic and technical

[5] A persistent and bioaccumulative substance that has been determined to be toxic or capable of being toxic under CEPA, that is present in the environment primarily from human activity, and that is not a naturally-occurring radionuclide or naturally-occurring inorganic substance, is required to be added to Schedule 1 and to be subject to the virtual elimination provisions of the Act.

[6] According to CEPA, “virtual elimination” means, in respect of a toxic substance released into the environment as a result of human activity, the ultimate reduction of the quantity or concentration of the substance in the release below the Level of Quantification (LoQ) specified in the Virtual Elimination List. The LoQ is the lowest concentration that can be accurately measured using sensitive but routine sampling and analytical methods (Canada 1999).

considerations (section 6.2 of this document) andin line with the proposed environmental objective, the proposed risk management objective will focus on the notification of any significant new activities that could result in a significantly greater quantity or concentration of mitotane being released to the environment, or that could lead to a significantly different manner or circumstances of exposure to mitotane, and to consider further risk management actions, if necessary.

## 3.3 Proposed risk management action

To achieve the proposed environmental and risk management objectives, the proposed risk management action being considered for mitotane is the **application of SNAc provisions[7] under CEPA** as a preventative measure. No risk management actions are being proposed to limit the essential use of mitotane as a therapeutic cancer drug.

Following the publication of this Risk Management Approach document, additional information obtained from the public comment period and from other sources will be considered, along with the information presented in this document, in the development of the SNAc Notice of Intent.

## 3.4 Risk management information gaps

The actual contribution of mitotane loading to the environment from its use as a therapeutic cancer drug is difficult to ascertain. As a prescription drug, mitotane may be released to wastewater and may be found in wastewater effluent and biosolids from wastewater systems as well as in water and sediments in proximity of local point source discharges. Although most releases to wastewater systems may be attributed to human excretion of the drug, run-off from agricultural fields, to which pesticides were historically applied, may also be discharged via wastewater systems' storm water effluent. Locations of wastewater systems receiving inputs of mitotane where patients may reside, or receiving inputs from hospitals or health care centers where mitotane may be administered, are not known but are expected to be geographically dispersed across the country. The use of pre-treatment methods or of dedicated wastewater systems at hospitals is not known, and the efficiency of wastewater

[7] A significant new activity is an activity that could result in a significantly greater quantity or concentration of the substance in the environment, or that could lead to a significantly different manner or circumstances of exposure to the substance. The SNAc provisions trigger an obligation for a proponent to notify and the government to assess, information about a substance when a proponent proposes to use the substance in a significant new activity. The assessment is completed by the Ministers, based on information provided by the notifier and other information available to them. If, based on the outcome of the assessment, the proposed new activity could pose a risk to the environment or human health, then the Ministers may consider further risk management action(s), if warranted.

systems in removing this substance is uncertain as wastewater systems are not typically designed to specifically remove pharmaceuticals.

To inform future assessment and risk management decision-making, it is important to identify any changes to the information reported since 2006. With the above information gaps in mind and the proposed SNAc instrument, the following information should be provided by December 27, 2017 to the contact details identified in section 8 of this document:

- Information on current or planned activities with the substance that could be used to inform the definition of 'significant new activities' in the development of the proposed SNAc instrument, such as, but not limited to:
    - Any manufacturing of mitotane or of mitotane-containing products in Canada (since 2006);
    - Any imports of mitotane into Canada (since 2006), other than quantities previously reported during the public comment period on the Risk Management Scope document published on July 6th, 2013; and
    - Any other use details in Canada (since 2006), beyond what is presented herein;
- Any information to address the information gaps, such as, but not limited to:
    - Any environmental monitoring information;
    - Any information as to potential methods and efficiencies of wastewater treatment systems (e.g. in removing this substance from wastewater effluent); and
    - Any additional information on this substance, beyond what is presented herein.

# 4. Background

## 4.1 Current use and identified sectors

Information was collected through a CEPA section 71 notice conducted for the 2005 calendar year (Canada 2006). The results indicated that mitotane was not manufactured in Canada; however, two companies imported mitotane into Canada in the 100–1,000 kg/year range (Environment Canada 2005).

For the 2006 calendar year, information gathered through a subsequent section 71 notice indicated that mitotane was not manufactured in, imported into or used in Canada in a quantity above the reporting thresholds; however, one Canadian company identified itself as having stakeholder's interest in the substance (Canada 2009a).

Recent information from the pharmaceutical industry indicates that actual use in Canada varies from year to year, but quantities are generally in the range of 100 to 1000 kg per year (Environment Canada 2013a).

In Canada, mitotane is registered in Health Canada's Drug Products Database (DPD) as an active ingredient in a licensed pharmaceutical drug (DPD 2010). This prescription drug is an oral chemotherapeutic agent, used in the treatment of cancer of the adrenal gland[8] (ATSDR 2002, CCS 2014, University of Michigan 2010). Specifically, mitotane is indicated in the treatment of inoperable, metastatic and recurrent adrenocortical cancers[9] (Attivi *et al.* 2010, Bristol-Myers Squibb 2010, Health Canada 2011a).

The exact number of adrenocortical cancer cases is not known and such cases may be reported in the general categories of other endocrine cancers or kidney cancer (e.g. in the United States National Cancer Institute's Surveillance, Epidemiology and End Results database, available at http://seer.cancer.gov/ or by the Canadian Cancer Society (CCS)). In 2010, 305 new cases of endocrine cancers were reported in Canada (CCS 2014).

Most clinicians consider mitotane the drug of choice for the treatment of adrenocortical cancers (ASHP 2010, Health Canada 2011a). An average daily dose of at least 8–10 grams is recommended by the distributor (Bristol-Myers Squibb 2010). Patients' response to mitotane is highly variable (Attivi *et al.* 2010). Until a stable regimen is found (i.e. the maximum tolerable dose is reached), the patient resides in the hospital (Bristol-Myers Squibb 2010). The recommended mitotane concentration in plasma (14–20 mg/L) is generally reached after a period of 2–3 weeks (Moy 1961). Afterwards, the patient is released from the hospital for the remainder of the treatment period, which varies between 4 and 48 months (Hutter and Kayhoe 1966, Baudin *et al.* 2001, Brunton *et al.* 2005, Terzolo *et al.* 2000, ASHP 2010, Attivi *et al.* 2010).

In other countries, mitotane has also been reported to be used to treat Cushing's syndrome (hyperadrenocorticism) in humans and dogs (ATSDR 2002, HSDB 2010).

The primary stakeholders relevant to this substance include:

- Pharmaceuticals sector, including manufacturers, importers and distributors; and
- Non-governmental health organizations and Canadians.

[8] The two adrenal glands are located above each kidney, deep inside the upper part of the abdomen. They are part of the body's endocrine system (CCS 2014).

[9] Malignant (cancerous) tumours of the adrenal gland are rare. It is more common for cancer in other parts of the body to spread (metastasize) to the adrenal gland than for cancer to start in an adrenal gland. The adrenal gland has an outer layer of gland tissue called the cortex and an inner layer of nerve tissue called the medulla. Cancer that starts in the cortex is called adrenocortical carcinoma (CCS 2014).

# 5. Exposure sources and identified risks

## 5.1 Sources and releases to the Canadian environment

Mitotane does not occur naturally. Presence in the environment mostly occurs from the past applications of the insecticide formulations, dichlorodiphenyltrichloroethane (DDT) and dicofol (PMRA 2007), and to some extent, through its current use as a therapeutic cancer drug.

As a therapeutic cancer drug, mitotane is ingested in tablets. According to the product monograph, retrieved from the DPD (2010), mitotane is absorbed in the body or converted to a water-soluble metabolite. Unchanged mitotane has not been found in urine or bile (US FDA 2009). The capacity of the intestine to dissolve the recommended daily dose of mitotane, as required for uptake, is limited. Since the information available on the fate and possible transformation of the unabsorbed product is limited and uncertain, it is conservatively assumed that 60% is excreted unchanged in the feces (Moy 1961). As a result, mitotane may enter wastewater systems, where it will preferentially partition to sludge, which may be transformed into biosolids. Mitotane is expected to be found in water and sediments in proximity of local point source discharges. The application of biosolids to agricultural fields is a potential point of entry of mitotane into soils in Canada.

However, most measured concentrations of mitotane reported in the final assessment in surface water, soil and sediments are expected to be from past applications of pesticides rather than from the current pharmaceutical use. In fact, for a large proportion of measured concentrations of the samples in all environmental compartments, mitotane was not detected. Given mitotane's tendency to settle into sediments and the limited use of this substance in Canada, high ambient concentrations in surface water are not expected (Canada 2017a).

## 5.2 Exposure of concern in Canada

As mitotane can be released to water,  an Environment and Climate Change Canada' spreadsheet tool, was used to estimate the substance concentration in multiple water bodies receiving wastewater treatment system effluent to which mitotane may have been released from the pharmaceutical use (Environment Canada 2013b).

As the therapeutic cancer drug is only prescribed to a limited number of patients in Canada, mitotane is expected to be released to only a few sites at any point in time. In addition, as the locations of the wastewater treatment systems receiving inputs of mitotane are unknown, the daily drug dose for a single patient was entered for each of the approximately 1000 sites in the spreadsheet tool to identify the fraction of sites that could potentially show a risk if there was use and

excretion of mitotane by one patient that resides in that area. The spreadsheet tool provides these estimates for approximately 1000 release sites across the country. The following assumptions[10] were used:

- loss to wastewater of 60% of the daily dose recommended for a single user;
- wastewater treatment system removal rate estimated at 87% for aerated and facultative lagoons, 54.6% for primary-only treatment and 68.1% for primary-secondary combined treatment;
- receiving water dilution factor in the range of 1 to 10;
- an average daily dose of 9 grams (Bristol-Myers Squibb 2010); and

Based on the 100–1000 kg reported, between 30 and 304 patients could be using the therapeutic cancer drug annually in Canada. Assuming a single patient per site in Canada, the number of patients that could be using the therapeutic cancer drug also represents the number of sites where the risk quotient analysis applies at one point in time. As a result, the predicted environmental concentration (PEC) of mitotane in the receiving water bodies was estimated to be in the range of 8.8E-5 to 0.25 mg/L (Environment Canada 2013b).

Based on data for approximately 1000 wastewater treatment systems, it is predicted that the PECs for mitotane may exceed the predicted no-effect concentration (PNEC)[11] in about 81% of the water bodies across Canada receiving wastewater effluent where a single patient using the therapeutic cancer drug may reside (Environment Canada 2013b). However, it is recognized that there is a limited number of patients using the therapeutic cancer drug in Canada at any time. Statistically, 81% of the areas where the estimated 30–304 patients reside may be at risk of potential ecological harm for aquatic organisms. If the assumption is made that each patient resides near a separate water body, then it is estimated that harm to aquatic organisms through the use of mitotane as a therapeutic cancer drug could occur in approximately 25 to 250 water bodies annually where wastewater effluent is discharged in Canada (Canada 2016a). Based on over 3700 Canadian wastewater systems (Environment Canada 2012a), this estimate represents less than 7% of all wastewater systems discharging into water bodies in Canada.

[10] The estimated concentrations of mitotate released to the environment are based on assumptions applied from its current use as a prescription drug. Presence in the environment from historical contamination from DDT and dicofol are not considered, and clinical use of mitotane accounts for all mitotane releases of the drug product.

[11] A PNEC was derived from the chronic toxicity, as the most sensitive experimental value for the analogue *p,p'*-DDD (CAS RN 72-54-8), for *Hyallela azteca.*

# 6. Risk management considerations

## 6.1 Alternatives and alternate technologies

Therapeutic options for inoperable or metastatic adrenocortical cancers are very limited. Furthermore, while other chemotherapy drugs may be used and clinical trials may be underway, these drugs or potential new agents are most often administered in conjunction with mitotane and not in its place. Currently, the prescribed use of mitotane remains the best option for the management of adrenocortical cancers (Health Canada 2011a).

No significant advances in the treatment of adrenocortical cancers have been developed (Roman 2006). Achieving therapeutic levels take time due to mitotane's poor solubility and low bioavailability (Terzolo *et al.* 2000). As a result, mitotane can be released to the environment via local wastewater systems by adrenocortical cancer patients. As such, methods to increase mitotane's bioavailability and solubility may decrease the time for the initiation of therapeutic activity and may also reduce the amount of mitotane released to the environment. Research on methods to improving patient response to mitotane is ongoing.

Alternate drugs and therapies

Mitotane is not the only therapeutic cancer drug prescribed for the treatment of adrenocortical cancers. However, most drugs used (e.g., streptozotocin, vincristine, dacarbazine and doxorubicin) are administered with mitotane (CCS 2014). Clinical trials are underway where treatment options do not require the use of mitotane. The development of new adrenocortical cancer treatments could reduce the need for the use of mitotane in the future. Most clinical trials are recorded by the United States National Cancer Institute (NCI) and include, for example, antineoplastons (NCI 2012a), miscellaneous inhibitors (Quinkler *et al.* 2008, Ye *et al.* 2010, Ayala-Ramirez *et al.* 2012, NCI 2012b, 2013a) and heated chemotherapy (NCI 2013b).

Hormonal excess may be a symptom of adrenocortical cancers that is often unresolved by inefficient chemotherapy efforts. Elevated levels of cortisol secretion can lead to steroidogenesis, which must be treated with inhibitors such as mitotane. Other than mitotane, there are several alternative steroidogenesis inhibitors which may be administered, such as the drugs ketoconazole, metyrapone and etomidate (Veytsman *et al.* 2009).

Therefore, despite the progress for new drugs and treatment methods, mitotane still remains the therapeutic cancer drug of choice for patients suffering from adrenocortical cancers. In the future, new methods of administration may benefit adrenocortical cancer patients and consequently decrease the amount of excreted levels of mitotane.

## 6.2 Socio-economic and technical considerations

Risk management actions are not being proposed or considered to limit the essential use of mitotane as a therapeutic cancer drug[12].

With regards to the release of mitotane from this drug use, patients may reside in hospitals for short periods of time before returning home for the remainder of the treatment period. Locations of hospitals, that can administer mitotane, and of wastewater systems receiving inputs of mitotane are expected to be geographically dispersed across the country. The use of pre-treatment or of dedicated wastewater systems at such hospitals and the efficiency of wastewater systems in general in removing mitotane are uncertain.

Pharmaceuticals and certain ingredients in personal care products (PPCPs) are generally not removed by conventional wastewater treatment processes. This is because PPCPs are typically more structurally-complex and non-biodegradable under standard wastewater treatment conditions. PPCPs may be removed with more advanced removal techniques (e.g., electrodialysis and advanced oxidation processes, such as ozonation, membrane bioreactors, powdered activated carbon adsorption, reverse and forward osmosis, and nanofiltration), in combination or as stand-alone and with varying success (Alturki 2013, Dodd *et al.* 2008, Escher *et al.* 2006, Esplugas *et al.* 2007, Söderberg 2008, Wang *et al.* 2009, Xue *et al.* 2012, Zhang *et al.* 2013). However, these come at a cost and none have been tested for the removal of mitotane (although the effectiveness with other cytostatic drugs[13] may be optimistic for the removal of this particular drug). Refer to section 7.1 of this document for more information on wastewater management in Canada.

In the case of hospitals, more concentrated wastewater effluent containing pharmaceuticals may be generated, requiring pre-treatment specifically designed for hospital wastewater to help achieve greater removal efficiency (e.g., coagulation-flocculation) (Suarez *et al.* 2009), or dedicated treatment prior to discharging to the environment (Mulder *et al.* 2012).

Furthermore, PPCPs in wastewater and in biosolids are emerging issues in Canada and abroad. A PPCPs Surveillance Network has been established to study the status of PPCPs in the surface waters of Canada. The objectives of this network include determining exposure levels, understanding the environmental

[12] In determining the preventive or control actions in relation to a substance, the Ministers is required to take into consideration any factor or information that, in the opinion of the Ministers, is relevant, including, environmental or health risks and any other relevant social, economic or technical matters.

[13] Cytostatic describes the way some cancer treatment drugs work. Most drugs that are used to treat cancer kill the cancer cells, in which case the word cytotoxic may also be used (Cancer Research UK 2013).

fate of these chemicals, and generating sufficient data to identify the risks associated with the release of these products to the environment (Environment Canada 2013c). Monitoring of emerging substances of concern is important in understanding the impact of these substances on the environment. Mitotane has not been specifically monitored under this program but a number of PPCPs (used in greater quantities than mitotane) have been detected in the environment and continue to be the focus of this network.

# 7. Overview of existing risk management

## 7.1 Related Canadian risk management context

Mitotane, as a therapeutic cancer drug, is regulated under the *Food and Drugs Act* (Canada 1985b) administered by Health Canada. This use is the only current known use in Canada. Unused drugs should be returned to pharmaceutical take-back programs, which exist in many provinces and territories in Canada (Health Canada 2011b).

Wastewater management

There are no existing Canadian risk management measures identified that are specific for controlling the releases of mitotane to the environment. However, while not specific to releases of mitotane from its drug use, it should be noted that the management of wastewater and biosolids is subject to various federal, provincial, territorial and municipal legislation in Canada.

At the federal level, Environment and Climate Change Canada administers the *Wastewater Systems Effluent Regulations* under the *Fisheries Act* (Canada 1985c, Canada 2012a, Environment Canada 2012a). The objective of these Regulations is to reduce the risks to ecosystem health, fisheries resources and human health by decreasing the level of harmful substances deposited to surface water from wastewater effluent. While the Canadian Food Inspection Agency regulates the sale and import of biosolids intended for use as a fertilizer or supplement under the *Fertilizers Act* (Canada 1985d) and *Fertilizers Regulations* (Canada 2009b).

Provinces and territories manage the maintenance and operation of wastewater systems and/or composting facilities as well as the processing, use and disposal of biosolids and other nutrient source, including land application, through a variety of acts, regulations, best management practices and guidelines. Various standards and information requirements must also be met to obtain approvals, permits or licenses. Municipalities typically have sewer use by-laws (CCME 2009, 2010). In addition, other organizations, such as the Canadian Council of

Ministers of the Environment's (CCME) and the Bureau de normalisation du Québec (BNQ)[14], have standards and guidelines in place that jurisdictions can use when developing policy or reviewing requirements related to wastewater systems and biosolids.

## 7.2 Pertinent international risk management context

There are no existing international risk management measures that were identified for controlling the releases of mitotane from its use as a therapeutic cancer drug to the environment.

## 7.3 Risk management context on the pesticide products DDT and Dicofol

A number of domestic and international risk management measures related to mitotane in pest control products that were historically used in Canada include:

<u>In Canada</u>

- The *Pest Control Products Act* (PCPA; Canada 1985a) administered by the Pest Management Regulatory Agency (PMRA):
    - In Canada, the use of DDT was restricted in 1970 and no longer registered after 1985 under the PCPA (CCME 1999), and
    - Dicofol was de-registered as a pesticide under the PCPA and has never been produced in Canada. Sales of dicofol were voluntarily discontinued in Canada in December 2008, and all uses of dicofol products expired in December 31st, 2011. Dicofol products can no longer be legally sold or used in Canada;
- The *Prohibition of Certain Toxic Substances Regulations* (Canada 2012b) pursuant to CEPA to prevent the potential for any non-pesticidal use of DDT (Environment Canada 2010a); and
- Management and remediation programs related to contaminated sites in Canada, which fall under federal, provincial or territorial government jurisdiction depending on site location (CCME 1997, Environment Canada 2012b).

<u>Internationally</u>

Beyond controls related to the pesticide DDT (such as London 1987, ATSDR 2002, Rotterdam Convention Secretariat 2004, Basel Convention Secretariat 2007, Stockholm Convention Secretariat 2004, 2008a,b), there are no existing

[14] CCME and BNQ publications are available at: http://www.ccme.ca/ and http://www.bnq.qc.ca/

international risk management measures that were identified for controlling the releases of mitotane to the environment.

# 8. Next steps

Industry and other interested stakeholders are invited to submit comments on the content of this Risk Management Approach document or to provide other information, that would help to inform decision-making (as outlined in section 3.4 of this document), prior to December 27, 2017.

Comments and information submissions on this Risk Management Approach document should be submitted to the address provided below:

Environment and Climate Change Canada
Chemicals Management Division
Gatineau Quebec  K1A 0H3
Tel: 1-800-567-1999 | 819-938-3232
Fax: 819-938-3231
E-mail: eccc.substances.eccc@canada.ca

Companies that have a business interest in mitotane are encouraged to identify themselves as stakeholders. Stakeholders will be informed of future decisions regarding mitotane and may be contacted for further information.

Following this public comments period, the Government of Canada will initiate the development of the proposed SNAc instrument. Comments received on the Risk Management Approach document will be taken into consideration in the development of this instrument. Consultation will also take place as this instrument is developed. The risk management action outlined in this document may also evolve through consideration of information obtained from Health Canada's proposed multi-stakeholder consultation on the improvement to existing or the development of new non-regulatory initiatives that mitigate the release into the environment of *Food and Drugs Act* regulated substances and products.

| Actions | Date |
|---|---|
| Electronic consultation on proposed Risk Management Approach document | October 28 to December 27, 2017 |
| Submission of comments on the proposed Risk Management Approach document, including additional studies or information | By December 27, 2017 |
| Response to comments on the proposed Risk Management Approach document | No later than the time of publication of the proposed instrument |
| Publication of the Notice of Intent for the proposed SNAc instrument | No later than October 28, 2019 |

| | |
|---|---|
| Formal public comment period on the proposed instrument | 60-day period from the publication of the proposed instrument |
| Publication of the final SNAc Order | No later than April 28, 2021 |

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