



Government  
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# **Risk Management Approach for Chlorhexidine and its salts**

Environment and Climate Change Canada

Health Canada

June 2019

**Canada**

## Summary of Proposed Risk Management

This document outlines the proposed risk management actions for chlorhexidine and its salts, which have been found to be harmful to the environment.

The screening assessment concludes that there is risk of harm to the environment from chlorhexidine and its salts, as they meet criteria under paragraph 64(a) of the *Canadian Environmental Protection Act, 1999* (CEPA). However, chlorhexidine and its salts did not meet the criteria under paragraph 64(b) or 64(c) of CEPA as they are 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 may constitute a danger in Canada to human life or health. More information on the Screening Assessment is available [here](#).

In particular, the Government of Canada is considering implementing a Code of practice under Section 54 of CEPA and an Environmental performance agreement (EPA) to minimize the release of chlorhexidine and its salts to the environment from the industrial use of these substances.

Moreover, because certain data gaps remain, the following information should be provided (ideally on or before August 28, 2019), to the contact details identified in section 8 of this document, to inform risk management decision-making:

1. Best management practices in place at facilities manufacturing or repackaging chlorhexidine-based products;
2. Socio-economic and technical impacts and benefits associated with the proposed risk management for these substances; and
3. Changes in use patterns subsequent to previous data collection initiatives (noted in section 4.2 of this document).

The risk management options outlined in this Risk Management Approach document may evolve through consideration of assessments and risk management options published for other Chemicals Management Plan substances as required to ensure effective, coordinated, and consistent risk management decision-making.

**Note:** The above summary is an abridged list of actions proposed to manage these substances and to seek information on identified gaps. Refer to section 3 of this document for more complete details in this regard. It should be noted that the proposed risk management actions may evolve through consideration of additional information obtained from the public comment period, literature and other sources.

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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 to the environment and/or harmful to human health as set out in section 64 of CEPA<sup>1,2</sup>, and if so to manage the associated risks.

A substance, chlorhexidine acetate (also known as chlorhexidine diacetate), Chemical Abstracts Service Registry Number (CAS RN)<sup>3</sup> 56-95-1, was identified as a priority for assessment under the Chemicals Management Plan. In July 2013, Health Canada and Environment and Climate Change Canada (ECCC) published a draft Screening Assessment Report (SAR) and Risk Management (RM) Scope for chlorhexidine diacetate (Canada 2013a, 2013b). At the time, chlorhexidine diacetate was proposed to be toxic under section 64 of CEPA due to potential concerns to the environment. It was noted that chlorhexidine diacetate is a salt, and dissociates in water to produce the acetate counterion and chlorhexidine. It is this dissociated chlorhexidine moiety that has the potential to cause acute and chronic harm to aquatic organisms at low concentrations (Canada 2013a).

Subsequent to the publications for chlorhexidine diacetate, significant new information became available regarding other potential sources of exposure to the chlorhexidine moiety. This information included quantities of chlorhexidine and its other salts in commerce, presence in products sold in Canada, and industry details related to the formulation of chlorhexidine-based products. As a result, the scope of the assessment was expanded to consider potential impacts on the environment and human health with respect to exposures from other potential sources of chlorhexidine.

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<sup>1</sup> 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.*

<sup>2</sup> 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 products available to consumers. A conclusion under CEPA is not relevant to, nor does it preclude, an assessment against the hazard criteria specified in the *Hazard Product Regulations*, which are a part of the regulatory framework for the Workplace Hazardous Materials Information System for products intended for workplace use. Similarly, a conclusion on the basis of the criteria contained in section 64 of CEPA does not preclude actions being taken under other sections of CEPA or other Acts.

<sup>3</sup> [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.

An updated draft screening assessment was published in August 2017 to more broadly address the chlorhexidine moiety by considering chlorhexidine and its salts, including, but not limited to, chlorhexidine (CAS RN 55-56-1), chlorhexidine diacetate (CAS RN 56-95-1), chlorhexidine digluconate (CAS RN 18472-51-0), and chlorhexidine dihydrochloride (CAS RN 3697-42-5) (Canada 2017a). All of these substances are on the *Domestic Substances List* (DSL) (ECCC 2015a), with the exception of chlorhexidine dihydrochloride, which is on the *Revised In Commerce List* (ICL) (R-ICL [modified 2017]) of the *Food and Drugs Act* (F&DA) (Canada 1985a).

The Chemical Abstracts Service Registry Numbers (CAS RNs), Domestic Substances List (DSL) names (or chemical names) and common names for chlorhexidine and certain chlorhexidine salts, are listed in Annex A.

## 2. Issue

Health Canada and Environment and Climate Change Canada conducted a joint scientific assessment relevant to the evaluation of chlorhexidine and its salts in Canada. A notice summarizing the scientific considerations of the screening assessment for these substances was published in the *Canada Gazette*, Part I, on June 29<sup>th</sup>, 2019 (Canada 2019a). For further information on the screening assessment for chlorhexidine and its salts, refer to the [screening assessment](#).

### 2.1 Screening assessment Conclusion

On the basis of the information available, the screening assessment concludes that chlorhexidine and its salts are toxic under paragraph 64(a) of CEPA because they are entering 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, 2019b). However, chlorhexidine and its salts did not meet the criteria under paragraphs 64(b) or 64(c) of CEPA as they are 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 may constitute a danger in Canada to human life or health. The assessment conclusion is applicable to chlorhexidine and its salts (but not limited to the salts listed in the report) (Canada 2019a).

The screening assessment also concludes that the chlorhexidine moiety meets the criteria for persistence, but does not meet the criteria for bioaccumulation, as defined in the *Persistence and Bioaccumulation Regulations* made under CEPA (Canada 2000).

The exposure source of concern, identified in the screening assessment, is the release of chlorhexidine and its salts to the environment via wastewater treatment systems from the industrial formulation of chlorhexidine-based

products. As such, this document will focus on these activities and exposure sources of concern (refer to section 5.2).

## **2.2 Recommendation under CEPA**

On the basis of the findings of the screening assessment conducted pursuant to CEPA, the ministers recommend that “chlorhexidine and its salts” be added to the List of Toxic Substances in Schedule 1 of the Act<sup>4</sup>.

The ministers have taken into consideration comments submitted by stakeholders during the 60-day public comment period on the draft Screening Assessment and Risk Management Scope documents.

As the ministers finalize the recommendation to add “chlorhexidine and its salts” to Schedule 1, risk management instruments must be proposed within 24 months from the date on which the screening assessment is published, and finalized within 18 months from the date on which the risk management instruments are proposed, as outlined in sections 91 and 92 of CEPA (refer to section 8 for publication timelines applicable to this group of substances).

## **2.3 Public Comment Period on the Risk Management Scope**

The Risk Management Scope document for “chlorhexidine and its salts”, which summarized the proposed risk management options under consideration at that time, was published on August 19, 2017 (Canada 2017c). 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 the [public comments summary](#).

# **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.

For chlorhexidine and its salts, the proposed objective is focused on addressing the exposure sources of concern outlined in section 5 of this document. As such, the proposed environmental objective is to reduce concentrations of the

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<sup>4</sup> 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 substance to the Priority Substances List for further assessment, or recommend the addition of the substance to the List of Toxic Substances in Schedule 1 of the Act.

chlorhexidine moiety in the aquatic environment to levels below the predicted no-effect concentration (PNEC) of 210 ng/L.

### **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, instruments and/or tools for a given substance or substances.

In this case, the proposed risk management objective is to reduce the total concentration or quantity of chlorhexidine in wastewater released from facilities formulating chlorhexidine-based products to levels that are protective of the environment, taking into account technical and economic feasibility and consideration of socio-economic factors.

### **3.3 Proposed Risk Management Actions**

To achieve the proposed risk management objective and to work towards meeting the proposed environmental objective, the Government of Canada plans to implement a Code of practice under Section 54 of CEPA and an Environmental performance agreement (EPA) to reduce the total concentration or quantity of chlorhexidine in wastewater released from industrial facilities that formulate chlorhexidine-based products.

Codes of practice are voluntary instruments that identify recommended procedures and practices or environmental controls relating to works, undertakings, and activities, including any subsequent monitoring activities. These set out official national standards that companies and organizations should follow (Canada 2017d). ECCC consults with stakeholders in the development of a code of practice. Such tools are not enforceable instruments, but may form the basis for enforceable instruments to be made in the future if need be (ECCC 2013). In this case, a code of practice would be developed and used to help industrial facilities that formulate chlorhexidine-based products reduce their impact on the environment through non-regulatory means.

An EPA is a voluntary and non-statutory instrument that allows parties with common goals to address a particular environmental issue. EPAs can address a wide variety of environmental issues affecting the environment and human health such as reducing the use or release of chemicals, promoting product stewardship or conserving sensitive habitats. They can be used to complement a regulation, a code of practice or a pollution prevention planning notice under CEPA.

#### Future Activities

Other activities to track changes in exposure or commercial use patterns associated with chlorhexidine substances may be considered in the future.

Note that the proposed risk management actions, described in this document, are preliminary and subject to change. Following the publication of this document, additional information obtained during the public comment period and from other sources will be considered, along with the information presented in this document, in the instrument development process<sup>5</sup>. The risk management actions outlined in this document may also evolve through consideration of assessments and risk management options published for other CMP substances to ensure effective, coordinated, and consistent risk management decision-making.

### 3.4 Performance Measurement

Performance measurement evaluates the ongoing effectiveness and relevance of the actions taken to manage risks from toxic substances<sup>6</sup>. The aim is to determine whether human health and/or environmental objectives have been met and whether there is a need to revisit the risk management approach for that substance, to ensure that risks are managed effectively over time. To achieve this, the Government of Canada will review, on a regular basis, the effectiveness of the risk management action(s) for chlorhexidine and its salts.

The Government of Canada plans to measure the effectiveness of the risk management action(s) by collecting and analyzing data, such as data on the release of chlorhexidine from industrial effluent to measure progress towards meeting the risk management objective.

In addition, the Government of Canada plans to collect and analyze data, including monitoring data obtained from the CMP Monitoring and Surveillance program and/or other initiatives on the presence of chlorhexidine and its salts in environmental media of concern (surface water and sediment). This data is intended to be collected to establish a baseline environmental presence, and also following implementation of risk management actions to measure progress towards meeting the environmental objective.

The results of performance measurement will be used to inform whether further risk management action is warranted and will be made available to Canadians, along with recommendations for further action, if applicable.

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<sup>5</sup> The proposed risk management regulation(s), instrument(s) or tool(s) is selected using a thorough, consistent and efficient approach and take into consideration available information in line with the Government of Canada's Cabinet Directive on Regulation (Canada 2018), the Red Tape Reduction Action Plan (Canada 2012a), and in the case of a regulation the *Red Tape Reduction Act* (Canada, 2015a).

<sup>6</sup> Performance measurement can be performed at two levels:

- Instrument-based performance measurement evaluates the effectiveness of an individual instrument in meeting the specific risk management objectives that were set out when the risk management tool was designed. The results of performance measurement will help determine if additional risk management or assessment is needed (*i.e.*, evaluate whether risk management objectives have been met); and
- Substance-based performance measurement considers performance of all final risk management instruments applied to a chemical substance and relevant data or indicators of exposure to the environment or human health (*i.e.*, evaluate whether human health and/or environmental objectives have been met).



### **3.5 Risk Management Information Gaps**

Interested stakeholders are invited to provide further information, such as outlined below, to inform risk management decision-making regarding chlorhexidine and its salts:

1. Best management practices in place at facilities manufacturing or repackaging chlorhexidine-based products;
2. Socio-economic and technical impacts and benefits associated with the proposed risk management for these substances; and
3. Changes in use patterns subsequent to previous data collection initiatives (noted in section 4.2 of this document).

Stakeholders are invited to provide this information on or before August 28, 2019 to the contact identified in section 8 of this document.

Should stakeholders have further information to help address these gaps, they should provide it ideally on or before August 28, 2019 to inform the risk management decision-making process, within the timelines (and to the contact) identified in section 8 of this document.

## **4. Background**

### **4.1 General Information on chlorhexidine and its salts**

Chlorhexidine and its salts do not naturally occur in the environment.

Chlorhexidine and its salts are broad-spectrum antiseptics used for sterilization, cleaning skin and hands, disinfecting wounds, and oral health, and are generally effective against a wide variety of bacteria, viruses and yeasts (Chemicaland21 2010, Cheminfo Services Inc. 2014). Chlorhexidine and its salts are also used as antimicrobial preservatives in cosmetics, natural health products, prescription and non-prescription drugs for human or veterinary uses (Block 2001).

Products containing chlorhexidine and its salts are also used as disinfectant products in hospitals, health care facilities, food premises, and farms; a subset of these products is available for consumer use (human and/or veterinary). Chlorhexidine and its salts are used in similar applications worldwide (PCPC 2013, ECHA c2007-2015a,b, European Commission 2016). More details on chlorhexidine-based product types and applications in Canada can be found in the screening assessment available [here](#).

## 4.2 Current Uses and Identified Sectors

In Canada, a number of companies manufacture or repackage chlorhexidine-based products. Most known or potential product formulators are located within or in the vicinity of the Toronto and Montreal metropolitan areas but not exclusively (Environment Canada 2015).

The primary industry sectors relevant to these substances include pharmaceutical and medicine manufacturing (North American Industry Classification System (NAICS) 3254, as well as soap, cleaning compound and toilet preparation manufacturing NAICS 3256).

Surveys have been conducted under section 71 of CEPA for chlorhexidine (reporting year 2011), chlorhexidine diacetate (reporting years 2005, 2006 and 2011), chlorhexidine digluconate (reporting year 2011), and chlorhexidine dihydrochloride (reporting year 2015). Voluntary information was submitted for chlorhexidine dihydrochloride for 2013 (Environment Canada 2015).

None of these substances were reported to be manufactured in Canada above the 100 kg per year threshold for the years reported. All of the chlorhexidine salts (diacetate, digluconate and dihydrochloride) were imported as a pure salt for processing/formulation into Canada during one or more of the reporting years. Chlorhexidine diacetate and chlorhexidine dihydrochloride were reported to be imported into Canada in quantities of 1000 to 10 000 kg, while imports of chlorhexidine digluconate were reported to be in the range of 10 000 to 100 000 kg (Environment Canada 2015). Chlorhexidine and its salts were also identified as being imported in products available to consumers.

## 5. Exposure Sources and Identified Risks

Releases of chlorhexidine and its salts to the Canadian environment come from the formulation of chlorhexidine-based products and their use by consumers, which are released to industrial and municipal wastewater. Releases are expected to be diffuse (i.e., down-the-drain from the use of products containing chlorhexidine or its salts), as well as from point sources (e.g., from sites formulating products containing chlorhexidine or its salts).

Since wastewater treatment technologies may only partially remove chlorhexidine, it may be released to surface water, and also to agricultural and pasture land soil through the application of biosolids (from wastewater treatment systems).

Chlorhexidine salts released to the aquatic environment will dissociate to release chlorhexidine, the moiety of concern. In the aquatic environment, chlorhexidine will bind to negatively-charged, dissolved and suspended solids and may settle in bed sediment, or be transported far from the source of releases.

The chlorhexidine moiety is expected to persist in water, soil and sediment. It has a low potential to bioaccumulate but has the potential to cause acute and chronic adverse effects to aquatic and benthic organisms at low concentrations.

Although no direct releases to soil are anticipated, indirect releases may result from the application to land of biosolids from wastewater treatment systems receiving wastewater that contains chlorhexidine. In soil, chlorhexidine may or may not be mobile, but could be transported via soil erosion or runoff (Canada 2019b).

## **5.1 Environmental Presence**

Data concerning concentrations of chlorhexidine and its salts in the Canadian environment have not been identified.

However, various wastewater treatment systems (WWTS) in Canada were sampled in 2016 and 2017 as part of the CMP Monitoring and Surveillance program. Influent and effluent samples were analyzed for chlorhexidine at 24 different WWTSs over the 2 year period (Canada 2019b). These WWTSs were selected to represent typical Canadian treatment systems and geographic variations. A total of 96 effluent samples were analyzed and chlorhexidine was measured in 19 of these samples. Concentrations ranged from 18.8 to 448 ng/L (laboratory reporting limits 11.5 to 12.1 ng/L).

Sampling was also conducted at some other wastewater treatment systems in Canada that receive industrial wastewater from facilities producing chlorhexidine-based products (Canada 2019b). Results do not necessarily correspond with production of chlorhexidine-based products at the time of sampling or, represent peak concentrations being released by facilities in a pulse (i.e., non-continuously). Measured concentrations of chlorhexidine in effluent samples ranged from 152 to 668 ng/L (n=15). The laboratory reporting limit was 11.5 ng/L.

Other jurisdictions have identified chlorhexidine as a potential concern in the environment due to its widespread use and have noted the need for further information on environmental concentrations (Boxall et al. 2005). Chlorhexidine has also been measured in wastewaters in Japan (Yamayoshi et al. 1981, Matsushima and Sakurai 1984, Kido et al. 1988, Kodama et al. 1988).

## **5.2 Releases and Exposure of Concern in Canada**

The exposure assessment estimated releases for two scenarios: from the industrial formulation of chlorhexidine-based products and the down-the-drain releases from the use of such products in Canada (Canada 2019b).

The results indicate that chlorhexidine and its salts may pose a risk to aquatic and benthic organisms when released as a result of industrial formulation of

chlorhexidine-based products, but not from down-the-drain releases as a result of the use of products containing these substances (Canada 2019b).

The formulation of chlorhexidine-based products generates wastewater during the cleaning of mixing and packaging equipment. The chlorhexidine-containing wastewater is discharged to a WWTS, which removes a certain fraction of the chlorhexidine. The chlorhexidine that is not removed at the WWTP is subsequently released to a receiving water body via wastewater effluent. Of note, releases associated with formulation may also occur in pulses due to batch processes or release of accumulated waste, which could result in higher acute exposures (Canada 2019b).

## 6. Risk Management Considerations

### 6.1 Alternatives

Although chlorhexidine-based products may be favoured for their broad-spectrum efficacy (McDonnell and Russell 1999), several antiseptics, antimicrobials and disinfectants not containing chlorhexidine salts are commercially available in Canada for both hard-surface disinfection and skin antisepsis (Atiyeh et al. 2009, DPD [modified 2015]). Several preservatives may also be used in cosmetics, natural health products, and non-prescription drugs for product preservation; some with applicable restrictions (Steinberg 2010, LNHPD [modified 2019]).

Searches in Health Canada's Drug Product Database indicate that triclosan, chlorhexidine and its salts, along with other active ingredients, may be used in some similar applications (DPD [modified 2018]). Health Canada and Environment and Climate Change Canada conducted a joint scientific assessment of triclosan (ECCC and HC 2016) which concluded that triclosan meets the criteria under paragraph 64(a) of CEPA as it is entering 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. The assessment also concluded that triclosan does not meet the criteria under paragraph 64(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 in Canada to human life or health. More information on Canada's assessment and risk management actions for triclosan can be found here:

<https://www.canada.ca/en/health-canada/services/chemical-substances/fact-sheets/chemicals-glance/triclosan.html>. Most other active ingredients that may be used in similar applications to chlorhexidine and its salts have not been assessed under CEPA.

More information on other substances assessed as part of the CMP is available on the Chemical Substances website at:

<http://www.chemicalsubstanceschimiques.gc.ca/>.

## 6.2 Technical Considerations

Guidance on good manufacturing practices has been found in literature for the drugs and cosmetics manufacturing sectors although they focus on product quality assurance and offer little in terms of environmental controls (Health Canada 2014, 2018).

In terms of wastewater treatment removal efficiencies, the characteristics of the wastewater treatment system and chlorhexidine's affinity for negatively-charged suspended solids will determine the degree to which chlorhexidine is associated with suspended solids or biological matter and removed from wastewater (Canada 2019b). Otherwise, pharmaceuticals and other personal care products<sup>7</sup> are generally resistant to conventional wastewater treatment as they are structurally complex and undergo limited biodegradation under standard wastewater treatment conditions, as may be the case for chlorhexidine (Kodama et al. 1988, Sugio and Kojima 1992, Study Submission 2010). This may create the need for pre-treatment or more advanced removal techniques (e.g., activated carbon filtration, advanced oxidation pre-treatments, reverse osmosis, nanofiltration, or membrane bioreactors) (Boxall et al. 2005, Clara et al. 2005, Dolar et al. 2012, Tekin et al. 2006). However, it does not prevent the use of other best management practices in lieu of or in addition to wastewater treatment (such as, but not limited to, recycling, re-use and disposal of water used for equipment, container and facility cleaning, where possible).

## 6.3 Socio-economic Context

Socio-economic factors have been considered in the selection process for the instrument respecting preventive or control actions, and in the development of the risk management objective. Socio-economic factors as identified in the *Cabinet Directive on Regulation (Canada 2018)*, Red Tape Reduction Action Plan (Canada 2012a) and the *Red Tape Reduction Act (Canada 2015a)* will be considered in the development of the instrument.

Most establishments involved in pharmaceutical and medicine manufacturing (NAICS 3254) in Canada are either micro (less than 5 employees) or small and medium enterprises (5 to 499 employees) (SMEs). Pharmaceutical sales in Canada have a 2.5% global market-share, making Canada the 9<sup>th</sup> largest world market. Total pharmaceutical sales in Canada were \$22 billion in 2013, with 89% sold to retail drug stores and 11% sold to hospitals. As of about mid-2014, the pharmaceutical manufacturing portion of the sector was valued at \$7.7 billion and employed 26 300 people, although growth and employment rates have been declining. More than half of Canada's pharmaceutical production is exported and

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<sup>7</sup> For the purpose of this document, a personal care product is defined as a substance or mixture of substances which is generally recognized by the public for use in daily cleansing or grooming. Depending on how the product is represented for sale and its composition, personal care products may fall into one of three regulatory categories in Canada: cosmetics, drugs or natural health products.

a significant portion of the Canadian market is supplied by foreign imports (ISED 2015, 2016a).

The soap, cleaning compound and toilet preparation manufacturing industry (NAICS 3256) is also predominantly comprised of micro or SMEs. For this sector, total number of production employees was 6 386 and manufacturing revenues were \$3.0 billion in 2012, although recent trends show this may be increasing (ISED 2016b).

## 7. Overview of Existing Risk Management

### 7.1 Related Canadian Risk Management Context

There are no existing Canadian risk management measures identified that are specific to controlling the releases of chlorhexidine and its salts to the environment.

A number of instruments exist under the *Food and Drugs Act*, administered by Health Canada, to limit the presence of chlorhexidine and its salts found in prescription and non-prescription drugs, natural health products and cosmetics (Health Canada [modified 2013], CIH [modified 2018], LNHPD [modified 2016], Health Canada 2018). Higher levels may be permitted but companies are required to submit safety and efficacy data to Health Canada for evaluation. Canadian drug manufacturers also have regulatory responsibilities and obligations when it comes to conducting licensable activities in compliance with regulations under the *Food and Drugs Act* to meet safety, efficacy, and quality requirements (Health Canada [modified 2017]). None of these requirements impose environmental conditions.

Furthermore, while not specific to releases of chlorhexidine and its salts, the management of wastewater systems, including biosolids, is subject to various federal, provincial, territorial and municipal legislations in Canada. At the federal level, ECCC administers the *Wastewater Systems Effluent Regulations* (WSER) under the *Fisheries Act* (Canada 1985b; Canada 2012b). The WSER require wastewater systems to achieve and maintain at least a level of secondary wastewater treatment. Chlorhexidine and its salts are not explicitly regulated in the WSER. In addition, the efficiency in removing these substances from wastewater will vary depending on the treatment type used at wastewater treatment plants.

Of note, the transportation of chlorhexidine and its salts is subject to the *Transportation of Dangerous Goods Act* and regulations, administered by Transport Canada (Canada 1992, 2001) and, if intended to be disposed of or recycled, to the *Export and Import of Hazardous Waste and Hazardous Recyclable Material Regulations* (Canada 2005) and *Interprovincial Movement of Hazardous Waste Regulations*, administered by ECCC (Canada 2002b).

## **7.2 Pertinent International Risk Management Context**

Although similar health controls also exist in other jurisdictions (EU 2008, 2009, ECHA 2014, European Commission 2014, US FDA 2016), no existing international risk management measures were identified for controlling the releases of chlorhexidine or its salts to the environment.

Chlorhexidine is included on the 2007 Organisation for Economic Co-operation and Development's list of High Production Volume chemicals (OECD 2009), indicating that it is produced or imported at levels greater than 1000 tonnes per year in at least one member country or region. The United States Environmental Protection Agency completed a Reregistration Eligibility Decision for chlorhexidine diacetate (as a pesticide active ingredient) in 1996 (US EPA 1996) and the substance, along with chlorhexidine digluconate, is currently under a registration review (US EPA 2011). Chlorhexidine and its digluconate salt have since been registered as part of the Registration, Evaluation, Authorisation and Restriction of Chemicals program in Europe. In particular, chlorhexidine (EC 200-238-7) has been registered for intermediate use only, and the digluconate salt (EC 242-354-0) has been registered for the manufacturing and/or importation in the European Economic Area in the 10 – 100 tonnes per year range (ECHA c2007-2015a, c2007-2015b).

In December 2017, the United States Food and Drug Administration (US FDA) issued a final rule regarding over-the-counter (OTC) health care antiseptics (US FDA 2017): 24 active ingredients (including chlorhexidine digluconate) used in non-prescription antiseptic products intended for use by health care professionals in a hospital setting or other health care situations outside the hospital were not generally recognized as safe and effective (GRAS/GRAE) by the FDA, because no additional data were submitted to demonstrate the safety and effectiveness of these ingredients. In effect since December 20, 2018, companies can no longer market health care antiseptics containing these ingredients; any such product require approval under new drug applications prior to marketing.

This rule applies to products such as patient antiseptic skin preparation, health care personnel hand wash, health care personnel hand rub, surgical hand scrub and surgical hand rub containing one or more of 24 specific active ingredients, including chlorhexidine digluconate (US FDA, 2017).

## **8. Next Steps**

### **8.1 Public Comment Period**

Industry and other interested stakeholders are invited to submit comments on the content of this Risk Management Approach or other information that would help to inform decision-making (such as outlined in section 3.5). Please submit additional information and comments prior to August 28, 2019.

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

Environment and Climate Change Canada  
Gatineau, Quebec K1A 0H3  
Telephone: 1-800-567-1999 (in Canada) or 819-938-3232  
Fax: 819-938-5212  
Email: [eccc.substances.eccc@canada.ca](mailto:eccc.substances.eccc@canada.ca)

Companies who have a business interest in chlorhexidine and its salts are encouraged to identify themselves as stakeholders. The stakeholders will be informed of future decisions regarding chlorhexidine and its salts and may be contacted for further information.

Following the public comment period on the Risk Management Approach document, the Government of Canada will initiate the development of the specific risk management instrument(s), where necessary. Comments received on the Risk Management Approach document will be taken into consideration in the selection or development of these instrument(s). Consultation will also take place as instrument(s) are developed.

## **8.2 Timing of Actions**

Electronic consultation on the Risk Management Approach: June 29, 2019 to August 28, 2019.

Publication of responses to public comments on the Risk Management Approach document: On or before June 2021

Publication of the proposed instrument(s): On or before June 2021

Consultation on the proposed instrument(s): 60-day public comment period starting upon publication of the proposed instrument(s)

Publication of the final instrument(s): On or before December 2022



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## ANNEX A. Chlorhexidine and certain salts

CAS RN	DSL name or chemical name	Common name
55-56-1 <sup>a,b</sup>	2,4,11,13-Tetraazatetradecanediimidamide, <i>N,N'</i> -bis(4-chlorophenyl)-3,12-diimino-	Chlorhexidine
56-95-1	2,4,11,13-Tetraazatetradecanediimidamide, <i>N,N'</i> -bis(4-chlorophenyl)-3,12-diimino-, diacetate	Chlorhexidine diacetate
3697-42-5 <sup>b</sup>	2,4,11,13-Tetraazatetradecanediimidamide, <i>N,N'</i> -bis(4-chlorophenyl)-3,12-diimino-, dihydrochloride	Chlorhexidine dihydrochloride
18472-51-0 <sup>a</sup>	D-Gluconic acid, compound with <i>N,N'</i> -bis(4-chlorophenyl)-3,12-diimino-2,4,11,13-tetraazatetradecanediimidamide	Chlorhexidine digluconate

<sup>a</sup> This substance was not identified under subsection 73(1) of CEPA but was included in this assessment as it was considered a priority based on other concerns.

<sup>b</sup> This substance is on the *Revised In Commerce List* of the *Food and Drugs Act* substances. Chlorhexidine dihydrochloride is not on the DSL or the *Non Domestic Substances List*.