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Final Screening Assessment of Chaetomium globosum strain ATCC 6205

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Synopsis

Pursuant to paragraph 74(b) of the Canadian Environmental Protection Act, 1999 (CEPA), the Minister of the Environment and the Minister of Health have conducted a screening assessment of Chaetomium globosum strain ATCC 6205.

C. globosum strain ATCC 6205 is a fungus that has characteristics in common with other strains of the species C. globosum. C. globosum is present in many environments. It has been isolated from natural settings such as soil, marine and fresh water, and in association with plants and animals. It is also found commonly on mouldy building materials. C. globosum has properties that are of potential use in biocontrol, plant growth promotion, biodegradation, water and wastewater treatment, drain cleaning and degreasing, and production of enzymes.

There have been no adverse environmental effects reported in the scientific literature that could be attributed C. globosum strain ATCC 6205. Members of the species are known to produce several mycotoxins and bioactive secondary metabolites, some of which are harmful to human cell lines and animals. Mycotoxin testing of C. globosum strain ATCC 6205 indicated that it produces low levels of mycotoxins relative to other C. globosum strains. There are a few reports of C. globosum acting as a pathogen in aquatic and terrestrial plants, invertebrates or vertebrates. In spite of these studies and reports and its widespread distribution in the environment, there is no evidence that C. globosum has adversely affected any terrestrial or aquatic species at the population level.

As a species, C. globosum is not known as a human pathogen. Despite its ubiquity, there have been only a few confirmed cases of systemic human infection with C. globosum, and these occurred in individuals predisposed to infection because of pre-existing health conditions. C. globosum has been implicated in nail and skin infections in otherwise healthy patients, often with a history of recent trauma to nail or skin as a predisposing factor. A number of antifungal agents including clotrimazole, isoconazole, and terbinafine are effective against C. globosum strain ATCC 6205 which may be used should an infection occur.

This assessment considers the aforementioned characteristics of C. globosum strain ATCC 6205 with respect to environmental and human health effects associated with consumer and commercial product use and in industrial processes subject to CEPA, including release to the environment through waste streams and incidental human exposure through environmental media. To update information about current uses, the Government launched a mandatory information-gathering survey under section 71 of CEPA, as published in the Canada Gazette, Part I, on October 3, 2009 (section 71 notice). Information submitted in response to the section 71 notice indicates that C. globosum strain ATCC 6205 is used in biodegradation, and research and development.

Based on the information available, it is concluded that C. globosum strain ATCC 6205 does not meet the criteria under paragraph 64(a) or (b) of CEPA as it 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. It is also concluded that C. globosum strain ATCC 6205 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.

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Introduction

Pursuant to paragraph 74(b) of the Canadian Environmental Protection Act, 1999 (CEPA), the Minister of the Environment and the Minister of Health are required to conduct screening assessments of living organisms added to the Domestic Substances List (DSL) by virtue of section 105 of the Act to determine whether they present or may present a risk to the environment or human health (according to criteria set out in section 64 of CEPA).[1] This strain was added to the DSL under subsection 25(1) of CEPA 1988 and the DSL under subsection 105(1) of CEPA because it was manufactured in or imported into Canada between January 1, 1984 and December 31, 1986.

This screening assessment considers hazard information obtained from the public domain and from unpublished research data generated by Health Canada[2] and Carlton University research scientists (McMullin and Miller, unpublished report 2016) as well as comments from scientific peer reviewers. Exposure information was obtained from the public domain and from a mandatory CEPA section 71 notice published in the Canada Gazette, Part I, on October 3, 2009. Further details on the risk assessment methodology used are available in the Risk Assessment Framework document "Framework for Science-Based Risk Assessment of Micro-organisms Regulated under the Canadian Environmental Protection Act, 1999" (Environment Canada and Health Canada 2011).

In this report, data that are specific to DSL-listed C. globosum strain ATCC 6205 are identified as such. Where strain-specific data were not available, surrogate information from literature searches was used. When applicable, literature searches conducted on the organism included its synonyms, and common and superseded names. Surrogate organisms are identified in each case to the taxonomic level provided by the source. Literature searches were conducted using scientific literature databases (SCOPUS, CAB Abstracts, Google Scholar and NCBI PubMed), web searches, and key search terms for the identification of human health and environmental hazards. Information identified up to November 2015 was considered for inclusion in this screening assessment report.

[1] A determination of whether one or more criteria of section 64 of CEPA are met is based on an assessment of potential risks to the environment and/or to human health associated with exposure in the general environment. For humans, this includes, but is not limited to, exposure from air, water and the use of products containing the substances. A conclusion under CEPA may not be relevant to, nor does it preclude, an assessment against the criteria specified in the *Hazardous Products Regulations*, which is part of the regulatory framework for the Workplace Hazardous Materials Information System (WHMIS) for products intended for workplace use.

[2] Testing conducted by Health Canada's Environmental Health Science and Research Bureau

Decisions from domestic and international jurisdictions

Domestic

C. globosum is not listed as a reportable or notifiable disease of aquatic animals under the Health of Animals Act, the Reportable Disease Regulations or the Health of Animal Regulations and it is not subject to any plant or animal health requirements according to Invasive Alien Species and Domestic Programs at the Canadian Food Inspection Agency (CFIA). This organism does not require a plant protection permit to be imported. However, given its potential to act as a very weak plant pathogen, CFIA requires the ‘basic’ plant pest containment level to be imposed should this organism be imported into Canada (CFIA, personal communication).

C. globosum is considered a Risk Group 1 organism for humans and terrestrial animals according to the Public Health Agency of Canada (PHAC, personal communication).

The National Public Health Institute of Quebec recommends biosafety containment level 2 when handling cultures of Chaetomium species (INSPQ, 2015)

International

Based on the U.S. Public Health Service Guidelines, ATCC designates C. globosum strain ATCC 6205 as a Biosafety Level 1 organism, not known to cause disease in healthy adult humans (ATCC, 2015).

C. globosum strain ATCC 6205 is considered a Risk Group 1 organism according to Germany’s Federal Institute for Occupational Safety and Health (BAuA, 2012).

1. Hazard assessment

1.1 Characterization of Chaetomium globosum strain ATCC 6205

1.1.1 Taxonomic identification and strain history

Binomial name: Chaetomium globosum

Taxonomic designation:

Kingdom: Fungi

Phylum: Ascomycota

Class: Sordariomycetes

Order: Sordariales

Family: Chaetomiaceae

Genus: Chaetomium

Species: Chaetomium globosum Kunze:Fries (Fries, 1829)

DSL strain: ATCC 6205

Synonyms, common and superseded names:

Chaetomium chartarum Ehrenb. 1818; Chaetomium chlorinum (Sacc.) Grove 1912; Chaetomium chlorinum var. chlorinum (Sacc.) Grove 1912; Chaetomium chlorinum var. rufipilum Grove 1912; Chaetomium coarctatum Sergeeva 1961; Chaetomium fieberi var. chlorina Sacc. 1877; Chaetomium fieberi var. rufipilum (Grove) Sacc. 1928; Chaetomium globosum var. arhizoides Dreyfuss 1976; Chaetomium globosum var. flavoviride E.K. Novák 1966; Chaetomium globosum var. globosum Kunze 1817; Chaetomium globosum var. griseum E.K. Novák 1966; Chaetomium globosum var. ochraceoides Dreyfuss 1976; Chaetomium globosum var. rectum Dreyfuss 1976; Chaetomium kunzeanum Zopf 1881; Chaetomium kunzeanum var. kunzeanum Zopf 1881; Chaetomium olivaceum Cooke and Ellis 1878; Chaetomium rectum Sergeeva 1961 and Chaetomium subglobosum Sergeeva 1960; Chaetomium globosum var. affine Tschudy; Chaetomium kunzeanum var. chlorina Sacc.; Chaetomium affine Corda, Icones fungorum hucusque cognitorum 1840; Chaetomium spirale Zopf 1881;Chaetomium cochlioides Palliser 1910; Chaetomidium barbatum Traaen 1914; Chaetomium subterraneum Swift and Povah 1929; Chaetomium ochraceum Tschudy 1937; Chaetomium fibripilium L.M. Ames 1950; Chaetomium mollipilium L.M. Ames 1950; Chaetomium lusitanicum M.R.M. Gomes 1953; Chaetomium coarctatum

Sergeeva 1961; Chaetomium spiculipilium L.M. Ames 1963 (Mycobank 2014) and Chaetomidium japonicum (teleomorph) (ATCC 2015 and Catalogue of Life 2014).

Strain history

C. globosum strain ATCC 6205 was originally isolated from stored cotton in Washington, DC, USA, in 1933 by H. Hunfeld. Later C. Thom at the U.S. Department of Agiculture obtained the strain from H. Hunfeld and afterwards it was designated with the strain number 459 of the U.S. Army Quartermaster Collection of Filamentous Fungi (curated by Emory Simmons). It was later transferred to the American Type Culture Collection in 1951 (CBS 2015) and has since been deposited in a number of other culture collections, as listed in Table 1-1.

Table 1-1: Listing of current strain designations for C. globosum strain ATCC 6205

Culture Collections	Strain Designations
American Type Culture Collection	ATCC 6205
Quartermaster Collection	QM 459
Bioresource Collection and Research Centre	BCRC 31605
Canadian National Mycological Herbarium	DAOM 84799
Centraalbureau voor Schimmelcultures (Netherlands)	CBS 148.51 and 161.52
Culture Collection, University of Göteborg (Sweden)	CCUG 26808
Colección Mexicana de Cultivos Microbianos	CDBB 252 and 902
Centre d'Etudes du Bouchet (France)	CEB 1218.1, 1218.2
Colección Espanola de Cultivos Tipo	CECT 2701
Leibniz-Institut DSMZ-Deutsche Sammlung von Mikroorganismen und Zelkulturen GmbH	DSM 1962
Fungal Genetics Stock Centre (University of Kansas)	FGSC 10151
Food Research Laboratory, Division of Food Research, CSIRO	FRR 1545, 2530 and 4486
IAM Culture Collection (Japan)	IAM 8059
International Collection of Microorganisms from Plants (New Zealand)	ICMP 7593
Institute for Fermentation, Osaka (Japan)	IFO 6347
Institute of Hygiene and Epidemiology-Mycology Laboratory (Belgium)	IHEM 3826
CABI Genetic Resource Collection	IMI 45550 ii, iii, iv and 362745
Japan Collection of Microorganisms	JCM 22615
Korean Collection for Type Cultures	KCTC 6279 and 6988
Mucotheque de L'Université catholique de Louvain (Belgium)	MUCL 1984 and 39889
National Institute of Technology and Evaluation	NBRC 6347
Agricultural Research Service Culture Collection	NRRL 1870

(Illinois, USA)	
University of Alberta Mold Herbarium and Culture Collection	UAMH 7578
Uppsala University Culture Collection of Fungi	UPSC 3159
VTT Culture Collection (Finland)	VTT D-81079

1.1.1.1 Phenotypic and molecular characteristics

Morphological properties

The species C. globosum is a mycotoxin-producing filamentous fungus that has spherical, ovoidal or obovoidal ascomata (175-280 µm in diameter). The peridium is brown and composed of textura intricata. Ascomatal hairs are numerous and usually unbranched, flexuous undulate or coiled (see Figure 1-1), septate, brownish and up to 500 µm long. Dimensions of clavate acsci are 30-40 µm × 11-16 µm and it contains 8 spores. Ascospores (9-12 µm × 8-10 µm × 6-8 µm) are limoniform in face view and bilaterally flattened. They are usually brownish in color and contain an apical germ pore (de Hoog et al. 2000). Images obtained from transmission electron microscopy of C. globosum ascospores shows that they have double-layered wall structures consisting of outer layers that are very thick (about 500 nm) and inner layers that are thinner (about 100 nm) (Nakayama et al. 2013).

Health Canada analysis also shows that when cultured on corn meal agar, C. globosum strain ATCC 6205 colonies initially appear as a cottony white growth. Maturing colonies present an olive colour with notable dark green foci. Colony sizes are reported in Table A- 1 in Appendix A. Microscopic examination of the mature colonies reveals lemon-shaped ascospores, central dark brown globose to-flask-shaped asci that contain the ascospores with ascomatal hairs consistent with the de Hoog et al. (2000) morphological description of the species.

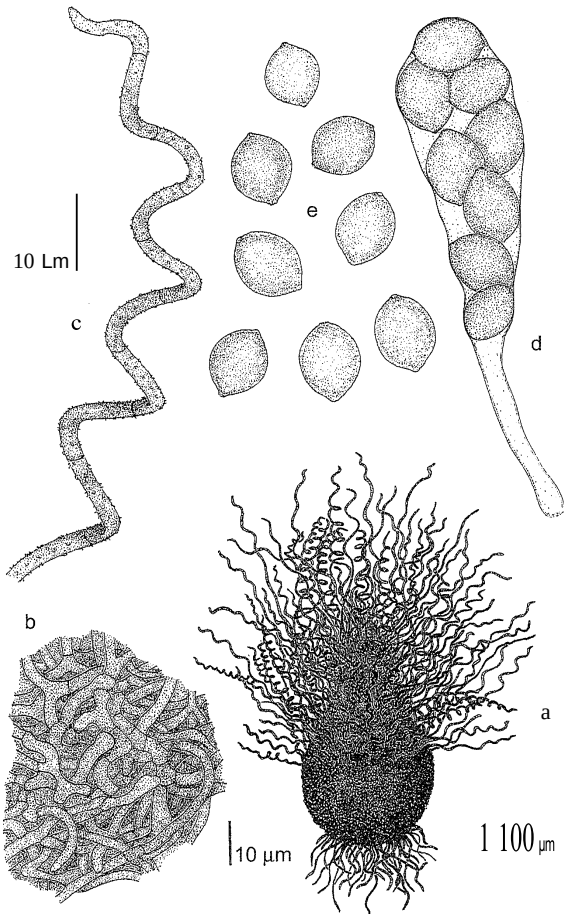

Figure 1- 1: Morphology of Chaetomium globosum, a. Ascoma; b. part of peridium; c. ascomal hair; d. ascus; e. ascospores (Taken from de Hoog et al. 2000 with permission).

Molecular properties

The draft genome sequence of C. globosum is estimated to be 34.3 Mb in size, with a percent guanine-cytosine (G+C) content of 55.6% and including an estimated 11,124 protein-coding genes (GenBank accession number: AAFU00000000) (Cuomo et al. 2015).

The rRNA gene sequences, containing internal transcribed spacers (ITS) 1, 2, 5.8S rRNA gene and the large subunit (LSU) region from C. globosum strain ATCC 6205 were determined and compared to both the Microseq® Fungal LSU D2 region v 2.0 library and the Ribosomal Database project release 11 LSU database by Health Canada scientists (Table B-1 in Appendix B). In order to determine similarity to other fungi the sequence was compared to the fungal 28S sequences in the Ribosomal Database Project. The results show that the top ten matches featured the LSU sequences of other C. globosum strains deposited at the Research Center for Pathogenic Fungi and Microbial Toxicoses, Chiba University, Chiba, Japan (Table B-2 in Appendix B).

The Microseq® database match results demonstrate that the DSL strain ATCC 6205 has highest sequence identity (99.68%) with the rRNA gene sequence of C. globosum CBS=145.38) and it shows high sequence identity with the rRNA gene sequences of Chaetomium species and Myceliophthora lutea. Among those, ATCC 6205 shows the highest sequence identity of 99.13 % with the rRNA gene sequence of Chaetomium brasiliense CBS=493.66. Nevertheless, the two species can be easily differentiated via their morphological characteristics as follows: C. brasiliense is characterized by cylindrical asci and ovate, bilaterally flattened ascospores at dimensions of 7-8.5 µm × 6-7µm × 5-6 µm. In contrast, C. globosum has clavate asci and biapiculate (lemon-shaped), bilaterally flattened ascospores measuring 9-12 µm × 7-9 µm (Guarro et al. 1995).

In another phylogenetic study of the partial LSU and the ITS regions of the rRNA genes of various Chaetomium species and using Bayesian and maximum likelihood analysis methods, ATCC 6205 is tightly positioned within the Chaetomium clade. The dendrogram also revealed that the ribosomal sequences of ATCC 6205 was nearly identical to other strains of C. globosum tested, including seven clinical strains of C. globosum (Bayesian probability of 1.0 and maximum likelihood of 91%), of which three were involved in systemic infections (isolated from blood, lymph node and mediastinum) and four were isolated from the nails and skin (de Hoog et al. 2013)(see

Figure B-1 in Appendix B). As such, the dendrogram shows that ribosomal sequence analysis (i.e., LSU and ITS) is not sufficient as a stand alone measure to differentiate C. globosum strain ATCC 6205 from clinical strains of C. globosum. This was also corroborated in a more recent study by Ahmed et al. (2016) involving several clinical isolates from the family Chaetomiaceae. Nonetheless, Beta-tubulin sequences show promise as markers for the resolution of C. globosum species either when used in conjunction with ribosomal sequences (Asgari and Zare 2011), or alone (Nakayama et al. 2013). Comparative analyses will be facilitated in the future, as whole genome sequences of C. globosum and environmental and clinical isolates will be reported.

1.1.2 Biological and ecological properties

1.1.2.1 Natural occurrence

C. globosum strain ATCC 6205 was originally isolated from cotton (NRRL, 2014).

Environmental strains of C. globosum have been isolated from a variety of habitats around the world. C. globosum has been isolated from soils (El-Said and Saleem 2008; Miller et al. 1957; Shanthiyaa et al. 2013), forest litter (Cha et al. 2011), and compost (Morey and Hoffman 2004), as well as from fresh water (Devi et al. 2009) and sea water (Kis-Papo et al. 2003).

C. globosum is present in and around human habitations. Spores of C. globosum have also been recovered from outdoor air dust particles (Abdel-Hafez et al. 1990), and residential indoor air (Ayanbimpe et al. 2010; Fogle et al. 2007). C. globosum is one of the three most common species of fungi on mouldy building materials, especially on

cellulose containing components such as wallboard, solid wood, textiles, manufactured wood, and ceiling tiles. It is also frequently found on insulation materials (reviewed in (McMullin et al. 2013). The organism has also been isolated from paper (Das et al. 1997).

1.1.2.2 Survival, persistence and dispersal in the environment

A variety of studies involving other C. globosum isolates suggest that the species has properties which allow survival, persistence and dispersal in the environment. However, no reports of survival, persistence and dispersal of ATCC 6205 were found in the literature.

In a soil microcosm persistence study, C. globosum CCFC008022 could be discriminated from other micro-organisms in the soil using quantitative PCR, targeting strain-specific non-coding regions in the genome. The study showed that if released into intact soil-core microcosms (at 22°C and 80% relative humidity) at initial densities of ~ 0.70 gram hyphal fragments per soil core, C. globosum CCFC008022 DNA concentrations decreased after day 2 and continued to fall to a minimum by day 14 (Hynes et al. 2006). The DNA concentration then increased after day 14 and persisted to the 126th day of incubation, when the study was terminated. At day 126 C. globosum DNA concentrations were 4-fold lower than levels measured on day 2, but remained higher at day 126 than at day 14 (Figure 1- 2). The fact that C. globosum remained detectable and persisted at the end of the experiment, suggests that this strain would survive for extended periods (i.e., the equivalent of at least one growing season), if released into nature.

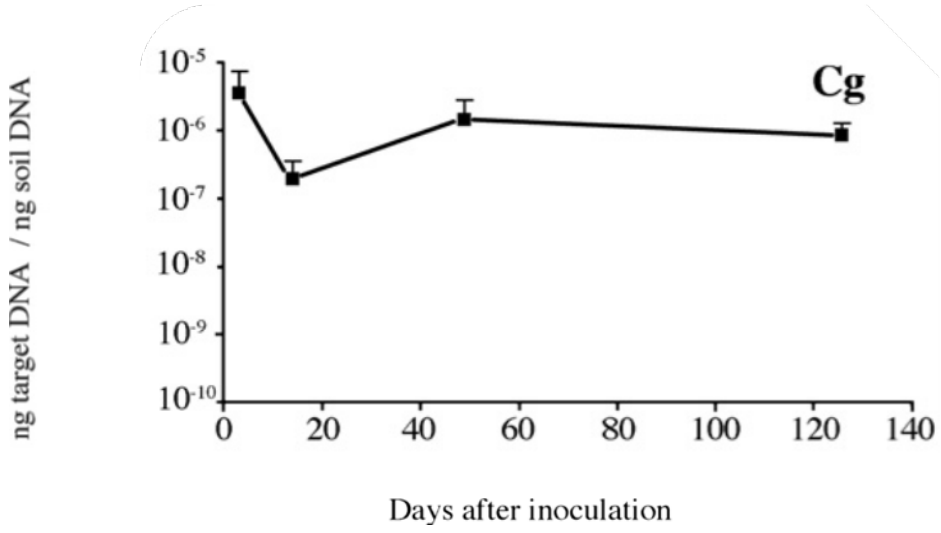

Figure 1- 2: Abundance (mean + SD) of Chaetomium globosum (Cg) DNA on post-inoculation days 2, 14, 49, and 126 in soil-core DNA extracts based on qPCR with strain specific primers (Taken from Can. J. Microbiol., 52, 451-461 with permission).

The growth of a soil isolate of C. globosum was studied under different conditions in a pot experiment that lasted one month (Tarafdar and Gharu 2006). The population growth was greater in sterile (16 fold) compared with non-sterile soil (12 fold). This observation suggests competing microbiota will limit the growth of C. globosum.

Spores of C. globosum can become airborne and are readily dispersible in the environment. Using quantitative PCR and specific primers, (Smith et al. 2012) detected viable C. globosum (CBS 145.38, best match at 98.9%) in two separate samples collected at a high altitude observatory. Kinematic back trajectory modeling suggested that air from these events probably originated from distant sources across the Pacific Ocean, including Asia.

Once dispersed into an environment, the ascospores of C. globosum are able to survive more than ten years without water (Steiman et al. 1997). They can resist adverse environmental conditions in part due to their thick, multilayered spore coat (Nakayama et al. 2013). The thermal death point for C. globosum spores is between 55°C and 57°C (Chapman and Fergus 1975), so environmental conditions in Canada are not expected to be limiting in this regard. No information was available about spore survival under low temperatures such as those encountered in Canada.

In fresh water, although it is not considered an aquatic fungus, C. globosum appears as a transient seasonal organism. Devi et al. (2009) showed that for C. globosum, the highest levels of occurrence in freshwater (18%) correspond with an adequate supply of nutrients, lower pollution levels and less human activity (Devi et al. 2009).

1.1.2.3 Life cycle

Sporulation of C. globosum can be influenced by a wide range of factors, including temperature, pH, relative humidity, and presence of nutrients. The formation of perithecia and ascospores in C. globosum ATCC 16021 appears to be favored in an acidic environment (preferentially at pH values ranging from 5.21 to 6.53, depending on the medium) and inhibited under basic conditions (pH values ranging 8.24 to 9.35) (Domsch et al. 1993).

At germination, globose vesicles form at the germ pores of the ascospores, which emit germ tubes that extend into a branching network of hyphae. Mycelia may similarly be produced by perithecial hairs or other hyphal fragments. In favourable conditions, an extensively branched mycelium develops within 6 to 12 hours (Chapman and Fergus 1975). Germination is also affected by temperature, pH and relative humidity.

The percentage of C. globosum spores that germinated following 12 hours of incubation at 25°C in malt extract agar, was highest at pH 4.9 (88%) and lowest at pH 3.5 (21%) (Chapman and Fergus 1975).

Spore germination in C. globosum occurs optimally between 24°C and 38°C. At 38°C, although germination happens and can reach to near maximum levels (91%), germ

tubes fail to elongate. The latent period before germination is also temperature-dependent, and at ideal temperatures, germination occurred within 3 hours (Chapman and Fergus 1975).

Soil studies show that C. globosum is a hydrophilic organism that requires a water activity of ≥ 0.94 for growth (Kouyeas 1964; Magan and Lynch 1986).

1.1.2.4 Growth conditions

The genus Chaemotomium features thermotolerant and thermophilic species that can grow at temperatures up to 40°C (Prokhorov and Linnik 2011). However, C. globosum strain ATCC 6205 grows optimally between 20°C and 30°C (minimum 5°C -10°C; maximum 30°C - 35°C) (Asgari and Zare 2011). In testing by Health Canada scientists using different types of media, C. globosum strain ATCC 6205 grew optimally at 28°C and 32°C and had a restricted growth at 37°C. No growth was seen at 42°C (see, Table A- 2 in Appendix A).

C. globosum isolated from sediments and dry microbial mats around Mexican salt ponds were considered weakly halo-tolerant. Following 10 days of incubation on malt extract agar plates supplemented with 25% NaCl, they showed a radial growth of not more than 2 cm (Cantrell et al. 2006). Conversely C. globosum strains isolated from the shore sands and water of the Dead Sea (DS) appeared to be adaptable to those highly saline environments. In vitro studies using those isolates showed that the C. globosum spores retained their viability in 80% diluted DS water for a period of 12 weeks. Vegetative mycelia of C. globosum also remained viable for up to 8 weeks in undiluted DS water and for 12 weeks in diluted DS water (50% and 10% of its original salinity) (Kis-Papo et al. 2003).

1.1.2.5 Nutrient cycling

C. globosum produces phosphatase and phytase which can promote availability of phosphorus to plants. In a field experiment, Tarafdar and Gharu (2006) showed that within 5-8 weeks of inoculation of soil with C. globosum, the activity of these phosphate mineralizing enzymes increased significantly in the rhizosphere of Pearl Millet (Pennisetum americanum): acid phosphatases (53%), alkaline phosphatases (72%), phytase (48%), and dehydrogenase (110%). Within 28 days, plants in inoculated soils had significantly higher phosphorus concentration in the shoots (19.29 mg/g vs. 16.45 mg/g) and roots (17.02 mg/g vs. 12.37 mg/g) than did plants in uninoculated soils. Enzyme level increases seen in the greenhouse portion of the study following inoculation of Wheat (Triticum aestivum) with C. globosum, further supported the results of the field study.

C. globosum can utilize a variety of carbohydrates as sources of carbon. See Table C-1 in Appendix C for the listing of the sources based on testing conducted at Health Canada. Prokhorov and Linnik (2011) reported C. globosum growth studies on wort agar, or mineral medium and either glucose, saccharose, mannite, lactose, amylum and

cellulose as carbon sources. For all carbon sources, fungal colony sizes increased on all media beyond three days and ascocarps formed on all media. In the environment, C. globosum uses natural sources such as cellulose in straw (Harper and Lynch 1985), the wood of the Europeam Beech (Fagus sylvatica) (Mohtashamipur and Norpoth 1990), heart wood and sapwood from the Brazilwood Tree (Caesalpinia echinata) (Silva et al. 2007), and fungal cell wall (Pythium ultimum) (Inglis and Kawchuk 2002). It is also capable of utilizing keratin in feathers (Kaul and Sumbali 1999) and collagen in leather (Strzelczyk et al. 1989).

1.1.2.6 Degradation of synthetic compounds

C. globosum is also able of degrading synthetic compounds such as polyesters (i.e., polycaprolactones, alone (Benedict et al.1983; Kim and Rhee, 2003) or blended with poly ethylene terephthalate (Chiellini et al. 1996), soybean oil-based polyurethane acrylate (Oprea and Doroftei 2011) as well as the pesticide Alachlor (2-chloro-2',6'-diethyl-N-(methoxymethyl) acetanilide), and its hydrolysis products including and not limited to 2-chloro-2',6'-diethylacetanilide and 2,6-diethylaniline (Tiedje and Hagedorn 1975).

1.1.2.7 Resistance to antibiotics, disinfectants and metals

C. globosum has different levels of susceptibility to a wide array of substances tested. These include mineral and organic salts, antimicrobial and antifungal compounds, pesticides and fumigants, preservatives, essential oils, bio-surfactants and industrial dyes (see Table D-1 in Appendix D).

In an antifungal sensitivity analysis involving 15 fungal isolates identified morphologically by the authors as C. globosum (7 clinical and 8 saprobic isoloates), all were resistant to both 5-fluorocytosine and fluconazole. None of the other tested agents (amphotericin B, itraconazole, ketoconazole or miconazole) were fungicidal; however, itraconazole, ketoconazole and miconazole were inhibitory (see Table D-2 in Appendix D) (Guarro et al. 1995). Another in vitro study testing sensitivity of 11 clinical strains of C. globosum to novel antifungal drugs, minimum inhibitory concentrations (MIC) of 0.26, 0.34, and 0.5 µg/mL were observed for ravuconazole, albaconazole and voriconazole respectively, indicating that they were generally active against C. globosum. However, the organism was resistant to micafungin with a MIC of 64 µg/mL (Serena et al. 2003).

C. globosum infections have been successfully treated with terbinafine (Aspiroz et al. 2007; Hubka et al. 2011), itraconazole (Hattori et al. 2000); and amphotericin B desoxicolate (Teixeira et al. 2003). Antifungal combinations have also been used. Itraconazole and miconazole were effective in combination (Falcón et al. 2009), and combination therapy with terbinafine and amorolfine was effective in one case (Kim et al. 2013) and ineffective in another (Yu et al. 2006). A canine case of C. globosum infection was also cured by ketoconazole (Sugiyama et al. 2008). See Table D-3 in Appendix D, for antifungal sensitivity analysis of some of the reported clinical cases.

C. globosum strain ATCC 6205 was tested against a number of antifungal agents by Health Canada scientists using three different methods (Table D-4, in Appendix D). While clotrimazole, isoconazole, and terbinafine were found to be effective against ATCC 6205, amphotericin, 5-fluorocytosine, griseofulvin, and nystatin were not effective at preventing growth of C. globosum strain ATCC 6205 at the maximum concentrations tested.

The European Committee on Antimicrobial Susceptibility Testing (EUCAST) have not yet provided breakpoints to denote the boundaries of susceptibility and resistance for Chaetomium species.

1.1.2.8 Toxigenic potential

C. globosum is capable of producing a variety of mycotoxins and secondary metabolites. Strains isolated from mouldy building materials from a number of locations across Canada primarily produce chaetoglobosins, chaetomugilin D and chaetoviridin A (McMullin et al. 2013a). Chaetoglobosins belong to the product class cytochalasan. They are antifungal, antibacterial, and cytotoxic (McMullin et al. 2013b), and distinguished by their biological mode of action, which is through interaction with the common target protein actin (Sekita et al. 1985). As a result, these metabolites are able to inhibit a variety of cellular movements, including cell division and motility, and causing change in cell shape (reviewed in Sekita et al. 1985). Chaetomugilins are potently cytotoxic and chaetoviridin A has antifungal properties (McMullin et al. 2013b). The latter two belong to the azaphilone product class (reviewed in Osmanova et al. 2010). Table E-2 in Appendix E provides a list of most researched mycotoxins produced by C. globosum along with their reported effects.

High performance liquid chromatography (HPLC) testing by McMullin and Miller (2016, unpublished study) revealed that crude filtrate extracts of ATCC 6205 contain chaetoglobosins A, C and F, chaetomugilin D and chaetoviridin A. ATCC 6205 produced approximately the same quantity of chaetoglobosins and azaphilones as lower producing strains previously studied by McMullin et al. (2013b), such as DAOM 240357 and DAOM 240358. See Table E-2 in Appendix E for the quantities of chaetoglobosins and azaphilones produced by ATCC 6205. ATCC 6205 also produced other minor chaetoglobosin isomers (528.2 Da), which could not be identified due to their small quantities and the absence of standards for comparison. These metabolites were suggested to be chaetoglobosin B, D or G, which are known to be produced by C. globosum (Udagawa et al. 1978). Other toxic metabolites such as chaetomin, cochliodinol or sterigmatocystin (a carcinogenic mycotoxin produced by some Chaetomium species) were not detected in the crude filtrate extracts of the DSL strain.

1.1.2.9 Immunologic characteristics

The genus Chaetomium is known to cause allergic reactions (topical and asthmatic) in sensitive individuals (Burge 1985).

Niedoszytko et al. (2007) found that 7% of an atopic population in Poland had an IgE response to C. globosum. A similar proportion to that found in West Virginia, USA (Beezhold et al. 2008). In a larger collection of human sera from throughout the USA, 2.5% had a strong IgE response to C. globosum and 3.1 % had a weak response (Provost et al. 2013).

Two chitosanases (45 kDa and 47 kDa) found on the surface of spores and in the culture filtrate of different strains of C. globosum were antigenic to rabbits and humans (Provost et al. 2013).

It is reasonable to assume that the DSL strain, ATCC 6205, could be capable of causing the immunological reactions mentioned above.

1.1.2.10 Horizontal gene transfer

There is evidence of widespread horizontal gene transfer among prokaryotes, and from prokaryotes to eukaryotes or vice versa; however, relatively few observations of horizontal gene transfer have been documented between fungi (reviewed in Khaldi et al. 2008). Horizontal acquisition of a bacterial gene by C. globosum, is hypothesized to be an ancient event (Gardiner et al. 2012; Khaldi et al. 2008).

1.1.3 Effects

1.1.3.1 Environment

Plants

C. globosum is an endophytic fungus that has been isolated from the roots and aerial parts of many terrestrial plants (see section 1.1.2.1, natural settings).

When barley (Hordeum vulgare) roots were grown in Murashige and Skoog (MS)-agar and inoculated with C. globosum (at a maximum quantity of 10^5 ascospores per seedling), the organism colonized the root tissue intercellularly and intracellularly up to the inner cortex and caused necrosis of the root. Nonetheless, the observed effect was shown to be dependent on the growth system used, where root tissue necrosis did not occur when the seedlings were exposed to the same quantity of the inoculant in an aeroponic culture system (Reissinger et al. 2003). Other than a previous report by the same author (Reissinger et al. 2001) where inculcation of barley roots with C. globosum under similar conditions showed discoloration of roots, a comprehensive literature search did not reveal any further reports of C. globosum causing disease in terrestrial plants.

C. globosum has been investigated for use as biocontrol organism that might be able to provide protection to terrestrial plants by antagonizing plant pathogenic fungi through the activity of its secondary metabolites and enzymes such as chitinases (Liu et al. 2008) and glucanases (Shanthiyaa et al. 2013). Antagonistic activity of possible use for

biocontrol has been demonstrated against a wide range of plant pathogens, including, Alternaria alternata (Li et al. 2013; Naik et al. 2009), Aspergillus niger (Sharma and Srivastava 2011), Cercospora sorghi (Li et al. 2011), Colletotrichum gloeosporioides (Soytong et al. 2005), Cochliobolus sativus (Aggarwal et al. 2004), Coniothyrium diplodiella (Zhang et al. 2013), Fusarium oxysporum (Charoenporn et al. 2010), Fusarium solani (Asran-Amal et al. 2010); Fusarium sulphureum (Li et al. 2011), Gloeodes pomigena (Davis et al. 1992), Fusarium graminearum (Ye et al. 2013), Nigrospora oryzae (Naik et al. 2009), Macrophomina phaseolina (Asran-Amal et al. 2010; Naik et al. 2009), Pestalotia species (Phong et al. 2014), Phoma sorghina (Naik et al. 2009), P. ultimum (Di Pietro et al. 1992), Phytophthora infestans (Shanthiyaa et al. 2013), Rhizoctonia solani (Asran-Amal et al. 2010; Awad et al. 2014; Naik et al. 2009), Rhizopus stolonifer (Zhang et al. 2013), Sclerotinia sclerotiorum (Kumar et al. 2013a), Sclerotinia rolfsii (Awad et al. 2014),Trichophyton mentagrophytes (Jiao et al. 2004) and Zygophiala jamaicensis (Davis et al. 1992).

In addition, plant growth promotion by C. globosum and C. globosum culture filtrates has been demonstrated. In a greenhouse study, treatment of Waito–C rice seedlings (deficient for gibberellin biosynthesis) with C. globosum strain LK4 culture filtrate (CF) significantly increased growth relative to positive controls, including increases in total length (18.26 ± 0.15 cm vs. 15.5 ± 0.29 cm), shoot length (11.5 ± 0.35 cm vs. 9.4 ± 0.32 cm) and shoot fresh weight (0.71 ± 0.10 g vs. 0.63 ± 0.19 g). Similarly, treatment of one week old chili pepper (Capsicum annuum) plants with CF containing propagules of C. globosum significantly increased shoot growth, chlorophyll content, plant biomass and leaf areas in the treated plants in comparison to the negative controls (exact values not provided, see Figure 3 in Khan et al. 2012). The growth promotion observed was thought to result from the production of gibberellins and indole acetic acid by C. globosum (Khan et al. 2012).

Inoculation of Wheat (T. aestivum), under greenhouse conditions, and Pearl Millet (P. americanum), under field conditions, with C. globosum, significantly increased plant growth and tissue phosphorus. In the greenhouse study, wheat biomass was higher by 25% and root length longer by 39% at day 28 post germination when inoculated, in comparison to the negative controls. The phosphorus concentration was also 10.5% higher in inoculated plants compared to negative controls. At crop harvest (day 63 post inoculation), the seed and straw yield of pearl millet was increased by 23 and 32%, respectively yield by 32% in the inoculated plants as compared to the negative controls. A significant improvement in plant (20%) and seed (25%) phosphorus content was also observed in the inoculated plants. The growth promotion effects observed were thought to be a result of the production of phosphatases and phytases, which helps mobilize phosphorus (Tarafdar and Gharu, 2006).

Invertebrates

C. globosum has been isolated from marine invertebrates. It was isolated from the gonads of the bivalve mollusks Modiolus modiolus and Crenomytilus grayanus. Although no signs of disease were observed in the mollusks, the authors characterized

C. globosum as a potential opportunistic pathogen of bivalve mollusks rendered immunocompromised by pollution (Zverera and Vysotskaya 2005). C. globosum has also been isolated from both healthy and diseased pacific sea fans (Eugorgia aurantiaca and Pacifigorgia eximia, respectively) in the tropical eastern pacific regions (Barrero-Canosa et al. 2013). However, the authors reporting these isolations did not make any conclusions regarding C. globosum's role in causing the effects observed in the diseased coral.

Experimental challenge of brine shrimp (Artemia salina) with crude C. globosum culture extracts, over a 24-hour exposure period, yielded an LC_{50} value of 7.71 µg/mL, approximately 3 times greater than that of the positive control, podophyllotoxin (LC_{50}=2.72 µg/mL) (Lu et al. 2009).

C. globosum has been observed in association with terrestrial invertebrates. It was presumed to be a secondary colonizer of wax moth (Galleria mellonella) cadavers based on a survey of insect-associated fungi in soils (Anwar et al. 2012; Sun et al. 2008).

Adverse effects of C. globosum mycotoxins in terrestrial invertebrates have been identified as part of experiments to assess its potential use in biocontrol. For example in vitro, C. globosum NK102 significantly repelled second-stage juveniles (J2s) of the Cotton Root-Knot Nematode (Meloidogyne incognita), both culture filtrates and chaetoglobosin A (ChA) caused 98% mortality after 72 hours in the J2s (LC_{50} of 77.0 µg/mL). In a greenhouse study, culture filtrates and purified ChA inhibited J2 penetration of cucumber (Cucumis sativus) seedlings. Treatment of the plants with 30 mg ChA per kg soil reduced by (63%) the number of nematode eggs per plant as compared to untreated plants (Hu et al. 2013).

Nematicidal activity was also observed against the northern root-knot nematode (Meloidogyne javanica). Larval mortality of 45% and 90% was observed 24 and 48 hours after in vitro treatment of the nematode larvae with 2.0 mL of undiluted C. globosum S-1 culture filtrate; however, culture filtrates of two other tested strains (S-2 and S-4) caused considerably weaker effects (23.3% and 25%, and 11.6% and 18.3% after 24 and 48 hours, respectively) (Qureshi et al. 2012).

Vertebrates

Few C. globosum infections have been identified in terrestrial vertebrates. Chaetomium species are part of the normal and seasonal cutaneous mycoflora of dogs (Cabanes et al. 1996); however, in a single case, C. globosum was isolated as the putative agent of infection in erythematous epilation in a juvenile dog. Other symptoms included elephantiasis-like hyperplasia and scales. The infection was successfully treated by oral and topical administration of ketoconazole (Sugiyama et al. 2008). C. globosum was identified as the causative agent of fungal pneumonia and death in a white stork (Ciconia ciconia) chick (Olias et al. 2010).

Adverse effects of mycotoxins produced by C. globosum have also been documented in experimental studies with animal models.

In a feeding study, the toxicity of corn inoculated with each of 53 isolates of C. globosum from different sources was tested in 21-day-old rats. Of the 53 tested isolates, 25 were lethal to the rats within 4 to 6 days following consumption of less than 5 grams of feed per animal, but only in feed incubated at least 4 weeks after inoculation with the fungus. Pre-mortem signs indicated damage to the central nervous system of the affected animals, and post-mortem lesions included hemoglobinuria, hemorrhagic enteritis, and subdural hemorrhage. Corn feed inoculated with a strain that was toxic to rats did not cause any detectable effects in pigs. An uncharacterized toxic fraction extracted from the corn feed was thought to be responsible for the effects seen in rats (Christensen et al. 1966).

Subcutaneous injection of chaetoglobosin A produced by C. globosum at 2 mg/kg body weight killed young Wistar rats, and in the inbred DDD strain mouse, LD_{50} values of 6.5 and 17.8 mg/kg body weight were estimated for male and female animals, respectively; however, oral administration of chaetoglobosin A at a dose of 400 mg/kg body weight caused little adverse effect on either mice or rats. Pathological examination of mice injected subcutaneously with 5 mg/kg body weight of the toxin revealed marked edema at the injection site which appeared several hours after injection and subsided in a week. In other tissues, necrosis of the thymus and spleen and degeneration of the spermatocytes in the testicles were noticeable (Ohtsubo et al. 1978).

C. globosum has also been observed in association with marine vertebrates. It was isolated from the gastrointestinal tract of the flat gray mullet (Mugil cephalus) with no indication of disease in the host (Yasuhide et al. 2008). C. globosum was also isolated from skin lesions (possible mycotic dermatitis) on the corpse of a stranded newborn southern right whale (Eubalaena australis). The calf’s body was otherwise in an excellent condition (Reeb et al. 2010).

A comprehensive scientific literature search did not reveal any further reports of ATCC 6205 or other putative strains of putatively identified as C. globosum in association with terrestrial or aquatic plants, invertebrates or vertebrates.

It is unclear to what extent the properties observed in other C. globosum strains are shared by C. globosum strain ATCC 6205; however, consideration of all effects attributed to the species provides an understanding of the spectrum of characteristics that ATCC 6205 may possess (both beneficial and harmful).

1.1.3.2 Human health

It is not clear if the concentration of mycotoxins produced in the course of natural contamination is sufficient to induce illness by the respiratory route (reviewed in Bush 2009). At least in the case of the chaetoglobosins, the route of exposure seems to be important: they are toxic by subcutaneous injection but not by ingestion.

Of the Chaetomium species reported in cases of human infection, C. globosum is most prevalent. In addition to skin and nail infections, systemic infections have been reported (Guarro et al. 1995). Nail and skin infections due to Chaetomium species occur predominantly in otherwise healthy patients following minor trauma to nails or skin, as a secondary infection, or in elderly people, with the infection typically progressing slowly (Hubka et al. 2011). C. globosum has a lower optimal growth temperature (optimum, 30°C) compared to other Chaetomium species, which may explain its prevalence in infections of cooler sites such as the nails and skin (Abbott et al. 1995).

The surface of human skin resists fungal infection due to the presence of the fungistatic free fatty acids and antagonistic bacterial flora; however, damage to these protective factors, presence of moisture, trauma and swollen cortical layer, support the colonization of pathogenic fungi (including Chaetomium species) that could entail a long-lasting infection (Tomšíková 2002).

C. globosum was the putative cause of minor skin infection, on the foot of a 46 year old man with no apparent history of trauma (Tullio et al. 2010), on the forearm of a 64 year old woman post trauma (Costa et al. 1988). A strain which had 99% sequence homology with ATCC 6205 in the ITS region was also shown to be the cause of skin infection and cellulitis on the foot of an 11-year-old girl (Tap et al. 2015). In all cases complete remission was gained following antifungal therapy.

Most fungi cannot infect a healthy nail organ, and only predisposing factors such as impaired blood circulation, peripheral neuropathy, diabetes mellitus, damage from repeated minor trauma, and limited immune defects as well as AIDS make the nail susceptible to fungal infection (Haneke 1991).

There are a number of case reports of nail infection (onychomycosis) caused by different strains of C. globosum in immunocompetent individuals with previous trauma at the site of infection (Aspiroz et al. 2007; Hubka et al. 2011; Latha et al. 2010; Hattori et al. 2000; Kim et al. 2013; Naidu et al. 1991) as well as in a mixed infection (Lagacé and Cellier 2012)), pre-existing eczema (Falcón et al. 2009; Hubka et al. 2011) and in extremes of age (Stiller et al. 1992). With the exception of three cases (Latha et al. 2010; Naidu et al. 1991 and Stiller et al. 1992) where the outcome was not reported, complete or near complete remission was reported following antifungal therapy.

There is a single report of an advanced case of subcutaneous phaeohyphomycosis caused by C. globosum in an immunocompromised 14-year-old child suffering from dilated cardiomyopathy. The case involved development of a painful erythema and necrosis on face and upper extremities. The patient died of heart failure during the course of antifungal therapy (Yu et al. 2006).

Infections with opportunistic fungi occur particularly among patients with hematological malignancies and acquired immunodeficiency syndrome (Guarro et al. 1995). In addition, C. globosum was implicated in systemic infections in two cases of bone marrow transplant recipients (Lesire et al. 1998; Texeira et al. 2003) (fatal in the former

case). It was also confirmed as the causative agent in two cases of fatal pneumonia in patients with acute myeloid leukemia (Paterson et al. 2005; Yeghen et al. 1996), in a case of invasive pulmonary mycosis in a patient suffering from Wegener's granulomatosis (Capoor et al. 2015) and in a case of peritonitis involving a patient receiving peritoneal dialysis in whereby resolution of the infection occurred after removal of the catheter (Barthez et al. 1984). Systemic infections in immune-competent individuals have not been reported.

Its restricted growth at 35°C, lack of growth at elevated temperatures, and its lemon-shaped ascospores set C. globosum apart from invasive Chaetomium species such as C. atrobrunneum, C. perlucidum and C. strumarium (Barron et al. 2003).

C. globosum is frequently isolated in buildings with poor indoor air quality (reviewed in Fogle et al. 2007). Inhaled fungal spores and mycelial fragments contain allergens, fungal glucan and low-molecular-weight toxins. Damp buildings have a higher percentage of spore and mycelial fragments. The majority of fungal biomass is present as fine fragments. Although the largest of these particles do not reach the lungs in high efficiency nor penetrate deeply, the smallest do so efficiently. The spores and sclerotia of toxigenic fungi typically contain very high concentrations of some or all of the toxins of that species. It has been suggested that a mechanism for health effects associated with fungal exposures in damp buildings was due to the impact of fungal metabolites on lung biology (Miller 1992).

In a case-control study involving occupants of water damaged buildings, C. globosum was one of four hydrophilic moulds associated with greater odds of respiratory illness such as asthma (i.e., interquartile range odds ratio of 1.45–2.19) (Park et al. 2008). Similarly, Patovirta et al. (2003) found an association between the occurrence of sinusitis in school teachers and elevated C. globosum-specific IgG from the blood sampled from individuals in a moisture-damaged school. The concentration of C. globosum-specific IgG (expressed as absorbance at a wavelength of 405 nm), was reported to be statistically different in subjects with and without sinusitis (0.473 and 0.223 respectively, $p = 0.044$). The number of sensitized, atopic patient sera that respond to a specific mould allergen typically correlates with the frequency that those species are found in damp buildings in Canada and the USA. Approximately 50 % of the sera tested responded to a C. globosum chitosanase (reviewed in Miller and McMullin, 2014).

1.2 Hazard severity

1.2.1 Environment

The environmental hazard potential of C. globosum strain ATCC 6205 is assessed to be low.

Although two reports by the same author show necrosis in barley root tissue, inoculated with C. globosum ascospores, there is no other evidence to suggest that C. globosum is

pathogenic to aquatic or terrestrial plants, despite its widespread distribution in the environment and well-documented association with terrestrial plants. In contrast, there is evidence to suggest that C. globosum has beneficial effects as a plant growth-promoting fungus with biocontrol activity against fungal plant pathogens.

C. globosum has been isolated from terrestrial and marine invertebrates including moth larvae, bivalve mollusks and sea fans, but there is no clear evidence that it causes disease in these hosts. C. globosum mycotoxins have produced effects under experimental conditions in pest nematodes (in biocontrol studies) and brine shrimp that were challenged with culture supernatants.

C. globosum has been isolated from terrestrial and marine vertebrates, both in the absence of disease, and in association with skin lesions in a juvenile dog and newborn whale and as the cause of fatal pneumonia in a stork. C. globosum mycotoxins are toxic to mice or rats exposed to high concentrations of C. globosum-infested feed, or directly exposed to its crude extracts or purified toxins as part of experimental investigations.

There is no evidence that C. globosum has adversely affected aquatic invertebrates or vertebrates at the population level in spite of its widespread distribution in the environment.

C. globosum-contaminated feed was toxic to rats, but not pigs, and only after the feed had been incubated at least four weeks with certain strains of C. globosum. Mycotoxin testing of C. globosum strain ATCC 6205 indicated that it produces low levels of chaetoglobosins and azaphilones relative to other C. globosum strains and that it does not produce sterigmatocystin or fusaproliferin. Despite the ubiquity of C. globosum in deteriorated plant material, including feeds, the mycotoxins produced by C. globosum are not considered agriculturally important (reviewed in Miller and McMullin, 2014).

1.2.2 Human health

The human hazard potential of C. globosum strain ATCC 6205 is assessed to be low.

Despite its ubiquity in natural and built environments, only five confirmed cases of systemic C. globosum infection have been reported, all in individuals with hematological malignancies or renal failure, of which three were fatal.

There are a number of reports of nail and skin infections caused by C. globosum, though it is not generally recognized as a dermatophyte. These cases were generally in otherwise healthy patients following minor trauma to nail or skin which may have facilitated infection. Most cases were responsive to antifungal therapy.

A number of antifungal agents including clotrimazole, isoconazole, and terbinafine are effective against the DSL strain C. globosum strain ATCC 6205 which may be used in the event of infection.

As mentioned in section 1.2.1, C. globosum-contaminated feed was toxic to rats when fed under experimental conditions. Mycotoxin testing of C. globosum strain ATCC 6205 indicated that it produces low levels of chaetoglobosins and azaphilones. Despite the ubiquity of C. globosum in deteriorated plant material, the mycotoxins produced by C. globosum are not considered agriculturally important.

Exposure to C. globosum is recognized as allergenic in humans and sensitization has been associated with respiratory illness in population studies.

Hazards related to micro-organisms used in the workplace should be classified under the Workplace Hazardous Materials Information System (WHMIS)[3].

2. Exposure assessment

2.1 Sources of exposure

This assessment considers exposure to C. globosum strain ATCC 6205 resulting from its addition to consumer or commercial products and its use in industrial processes in Canada.

C. globosum strain ATCC 6205 was added to the DSL in 1997 because it was manufactured in or imported into Canada for use in consumer or commercial products between January 1, 1984 and December 31, 1986.

Responses to a voluntary questionnaire, sent in 2007 to a subset of key biotechnology companies in Canada, combined with information obtained from other federal regulatory and non-regulatory programs, indicate that up to 14650 kg of products potentially containing C. globosum strain ATCC 6205 (formulation and concentration unknown), were imported into Canada in 2006 for domestic and industrial uses including drain cleaning and degreasing, as a septic tank or RV tank additive and for wastewater treatment.

The Government conducted a mandatory information-gathering survey under section 71 of CEPA, as published in the Canada Gazette, Part I, on October 3, 2009 (section 71 notice). The section 71 notice applied to any persons who, during the 2008 calendar year, manufactured or imported C. globosum strain ATCC 6205, whether alone, in a

[3] A determination of whether one or more criteria of section 64 of CEPA are met is based on an assessment of potential risks to the environment and/or to human health associated with exposure in the general environment. For humans, this includes, but is not limited to, exposure from air, water and the use of products containing the substances. A conclusion under CEPA may not be relevant to, nor does it preclude, an assessment against the criteria specified in the *Hazardous Products Regulations*, which is part of the regulatory framework for the Workplace Hazardous Materials Information System (WHMIS) for products intended for workplace use.

mixture, or in a product. Responses indicated that approximately 52 grams (equating to 5×10^3 CFU) of products containing C. globosum strain ATCC 6205 were imported in Canada in 2008 mainly for research and development.

The 2007 and 2009 surveys differed significantly in target and scope. In this assessment, results from the 2009 survey were used to estimate exposure from current uses because it requested information on uses of the micro-organism strain that is listed on the DSL, whereas the 2007 survey asked about uses of the products that had been associated with the micro-organism at the time it was nominated to the DSL. Because product formulations may have changed, information from the 2009 survey may more accurately represent current uses. Uses reported in the 2007 voluntary survey were also considered in the assessment of potential uses.

C. globosum strain ATCC 6205 is available for purchase from the ATCC. As it is on the DSL, and so can be used in Canada without prior notification, it may be an attractive choice for commercialization. A search of the public domain identified the following ongoing commercial and industrial applications of different naturally occurring C. globosum strains.

C. globosum has been used as an active ingredient in biocontrol products:

- Against Drechslera sorokiniana, the spot blotch of wheat crop (Product Sheet A-1, 2015).
- Against P. infestans, the cause of late blight of potato (Product Sheet A-2, 2015).
- As a broad spectrum fungicide for plant disease control (Soytong et al. 2001).

However, neither the living organism, nor its toxins are currently registered as pesticides in Canada.

C. globosum is also named as part of the formulation of the homeopathic remedies (Product Sheet C-1, 2015; Product Sheet C-2, 2015); however, it does not appear in the Natural Health Product Ingredient Database of Health Canada as an acceptable ingredient in homeopathic medicines.

C. globosum strain ATCC 6205 could be used as a production organism for a variety of enzymes, e.g., cellulase, β-1,4-glucan-4-glucanohydrolase (BCCM, 2014) and gluconase (ATCC, 2015).

C. globosum could potentially be used to colonize a particular environment and perform a specific function in situ, such as degradation of organic compounds (Xu 2015), waste digestion (Iyengar and Bhave 2006), to clean up waterways and irrigation sources, as well as for plant growth promotion (Product Sheet B 2014).

Other known and potential applications include use in diagnostic microbiological procedures such as:

- Fungal resistance testing in various materials (ATCC 2015; BCCM 2014);
- Aerosols testing (ATCC 2015; BCCM 2014);
- Slimicide evaluation (ATCC 2015; BCCM 2014);
- Sterility assurance testing (ATCC 2015);
- Efficacy testing of microbial remediation agents (Dixit and Tumala 2013);

Sources of exposure to mycotoxins produced by C. globosum strain ATCC 6205

The numbers of C. globosum strain ATCC 6205 introduced in the Canadian environment resulting from its addition to consumer or commercial products, and its use in industrial processes in Canada is expected to decline (Hynes et al. 2006) to levels comparable to resident strains of C. globosum because of limited carbon availability in soil, and competition and antagonistic activities of other micro-organisms (de Boer et al. 2003).

Despite the ubiquity of C. globosum in deteriorated plant material, including feeds and foods, and its ability to produce a number of potentially significant metabolites (Sekita et al. 1981), the mycotoxins produced by C. globosum are not considered agriculturally important (reviewed in Miller and McMullin 2014). Andersen and Thrane (2006) did not find C. globosum among the organisms recognized for fungal spoilage of fruit and cereals in Europe. Even though Pitt et al. (1994) found C. globosum among the species infecting cashew kernels in Thailand, no contamination of nuts or oil seeds with C. globosum mycotoxins, has been reported in Canada.

Chaetoglobosins that are listed among the mycotoxins associated with feeds and foods originate primarily from non-Chaetomium species such as Penicillium expansum and Penicillium discolor. C. globosum is not considered a significant source of these toxins in feeds or foods (Frisvad et al. 2006). Mycotoxin analysis of strain ATCC 6205 showed that in comparison with other C. globosum strains, it produced chaetoglobosins at low levels (see section 1.1.2.8 and Table A-10; McMullin and Miller, 2016 unpublished study). Similarly the major producers of sterigmatocystin and fusaproliferin in feeds and foods are Aspergillus and Fusarium species respectively (Frisvad et al. 2006). C. globosum is considered only a minor producer of these toxins, and analysis of strain ATCC 6205 did not show production of sterigmatocystin or fusaproliferin (McMullin and Miller, 2016 unpublished study). As such, any contribution of C. globosum to these mycotoxins in feed or food is expected to be negligible compared to levels already present through activities of other toxigenic fungi. A comprehensive search of the publically available information did not locate any recall of food or feed in Canada, precipitated by the presence of C. globosum or its mycotoxins. In addition, the mycotoxins detected in the DSL strain ATCC 6205 have not been subject to surveillance by the CFIA (CFIA 2016).

Another potential source of exposure to C. globosum strain ATCC 6205 mycotoxins is by inhalation directly through releases associated with industrial activities. Toxin exposure can also occur indirectly through exposure of the occupants of water-damaged buildings where ATCC 6205 has established subsequent to industrial release.

Another source of indirect exposure to the mycotoxins of the DSL strain would be exposure to construction waste subsequent to the buildings' demolition. Its ability to colonize moisture-damaged buildings is expected to be no better than that of resident strains of the species. As mycotoxin analysis of strain ATCC 6205 showed that in comparison with other C. globosum strains, it produced chaetoglobosins at low levels (see section 1.1.2.8 and Table E-1; McMullin and Miller 2016, unpublished study), releases of ATCC 6205 are not expected to significantly increase the levels of C. globosum mycotoxins above the background levels already present in moisture-damaged buildings.

A comprehensive search on the publically available data did not locate any information on the persistence of C. globosum's mycotoxins in the environment.

2.2 Exposure characterization

2.2.1 Environment

The overall environmental exposure estimation for C. globosum strain ATCC 6205 is low based on responses to the section 71 notice, in which reported uses are limited to research and development. Nevertheless, given the range and scale of known and potential applications of the species C. globosum strain ATCC 6205 listed in Section 2.1, there is potential for an increase in environmental exposure to products containing C. globosum strain ATCC 6205, and exposure scenarios arising from these products have been considered.

Should potential uses identified in Section 2.1 be realized in Canada, terrestrial species including plants, invertebrates and vertebrates could be exposed to C. globosum strain ATCC 6205 as a result of subsequent run off from uses such as waste digestion, biodegradation or as a biocontrol agent.

Release of living C. globosum strain ATCC 6205 from facilities performing diagnostic microbiological procedures, manufacturing enzymes and homeopathic products could occur but is expected to be limited by the application of good laboratory and good manufacturing practices. Exposure of environmental species to the micro-organism via facility release is expected to be limited.

Aquatic species, including plants, invertebrates and vertebrates are expected to be exposed to C. globosum strain ATCC 6205 through down-the-drain uses such as released wastewater effluents subsequent to waterway clean up, waste water treatment, drain cleaning or degreasing. In addition, aquatic species could be exposed to run-off subsequent to application in soil. By far, the exposure potential on aquatic species is expected to be most important, should the reproduction and growing conditions be met in the receiving water body. Down-the-drain applications such as those named above are more likely to result in exposure, since 100% of the micro-organisms are reaching the wastewater treatment plant. However, water treatment

processes (e.g., coagulation, flocculation, ozonation, filtration and chlorination) are expected to effectively eliminate these micro-organisms.

The extent of exposure to C. globosum strain ATCC 6205 will depend on the mass or volume released, on its persistence in the receiving environment, and on the proximity of environmental species to the sites of application or disposal.

Once released into nature the micro-organism may survive for more than four months in terrestrial environments, and could migrate from the point of introduction through hyphal growth or via runoff, but dispersal is expected to be predominantly through sporulation (Hynes et al. 2006). Spores could also be lifted from soils recently treated with C. globosum strain ATCC 6205 and may be readily dispersible in the environment (Smith et al. 2012). Consequently, they could be carried or inhaled by environmental species and establish where conditions are favourable, thereby widening the area in which terrestrial species could be exposed. Once dispersed into an environment, the ascospores of C. globosum are able to survive for more than ten years without water (Steiman et al. 1997). Nevertheless, once spores germinate, survival of vegetative state of C. globosum strain ATCC 6205 in soil will likely be limited by the presence of competing microbiota.

C. globosum appears as a transient seasonal organism in fresh water and is therefore unlikely to persist in aquatic environments (Devi et al. 2009).

2.2.2 Human

The overall human exposure estimation for C. globosum strain ATCC 6205 is low based on responses to the section 71 notice, in which reported uses are limited to research and development. Nevertheless, given the range and scale of known and potential applications of the species C. globosum strain ATCC 6205 listed in Section 2.1, there is potential for an increase in environmental exposure to products containing C. globosum strain ATCC 6205, and exposure scenarios arising from these products have been considered.

Should potential uses identified in Section 2.1 be realized in Canada, human exposure to C. globosum strain ATCC 6205 as a result of use in homeopathic medicine applications is expected to be minimal. Furthermore, standards for the preparation of homeopathic medicines require that the active ingredients are sterilized and/or serially diluted with alcohol, so exposure to the living organism from this use is not expected.

Direct human exposure to live C. globosum strain ATCC 6205 would be greatest through the direct use of consumer products containing ascospores or viable cells of the micro-organism. Handling and application of such products would be expected to result in direct exposure to aerosolized droplets or airborne spores via dermal or inhalation routes. Inadvertent ingestion following use on or near food preparation surfaces and contact with the eyes, are possible secondary routes of exposure.

The general population could be exposed as bystanders during commercial application of drain cleaning, waste water treatment, biocontrol or biodegradation products. The extent of bystander exposure will depend on the mode of application, the volume applied and the proximity of bystanders to the site of application. In general, exposure is expected to be low for these applications.

Indirect exposure to C. globosum strain ATCC 6205 in the environment subsequent to its use in wastewater treatment, cleaning up of water ways and irrigation systems, drain cleaning and degreasing of sewer lines, or disposal of waste from its use in the production of enzymes and homeopathic products is also likely to occur in the vicinity of application or disposal sites, but is expected to be less than direct exposure from the use of the micro-organism in consumer products.

In the event that C. globosum strain ATCC 6205 enters municipal drinking water treatment systems through release from intended and potential uses, drinking water treatment processes (e.g., coagulation, flocculation, ozonation, filtration and chlorination) are expected to effectively eliminate these micro-organisms.

Release of C. globosum strain ATCC 6205 from facilities manufacturing enzymes or homeopathic products could occur, but is expected to be limited by the application of good manufacturing practices, in which measures should be taken to minimise the probability of releases during production of the micro-organisms.

Human exposure to C. globosum strain ATCC 6205 from potential future uses could be medium from the use of consumer products, and low for indirect exposures subsequent to environmental release. Growth in the market for “greener” microbial-based products may increase human exposure to the DSL C. globosum strain which have potential applications in these products.

3. Risk characterization

In this assessment, risk is characterized according to a paradigm whereby a hazard and exposure to that hazard are both required for there to be a risk. The risk assessment conclusion is based on the hazard, and on what is known about exposure from current uses.

Hazard has been estimated for C. globosum strain ATCC 6205 to be low for the environment and low for human health.

The determination of risk from current uses is followed by consideration of the estimated hazard in relation to foreseeable future exposures (from new uses).

Risk from C. globosum strain ATCC 6205

Human and environmental exposure to C. globosum strain ATCC 6205 is estimated to be low because only small quantities and limited uses were reported in the section 71

survey. Therefore the risk associated from this organism for its current uses is estimated to be low.

Risk from mycotoxins produced by C. globosum strain ATCC 6205

As described in Section 2.1 Sources of Exposure, exposure to mycotoxins produced by C. globosum strain ATCC 6205 subsequent to its addition to consumer or commercial products or its use in industrial processes in Canada is expected to be low. Introduced populations of metabolically active C. globosum strain ATCC 6205 are expected to decline to levels comparable to resident strains of C. globosum. C. globosum produces low quantities of chaetoglobosins, sterigmatocystin and fusaproliferin relative to other toxigenic species (Penicillium, Aspergillus and Fusarium). Mycotoxin analysis of ATCC 6205 indicated that it produces low levels of chaetoglobosins and azaphilones relative to other strains of the species, and does not produce sterigmatocystin and fusaproliferin. Based on low exposure, and limited information suggesting a hazard from C. globosum mycotoxin in feeds, foods, or water-damaged buildings, the risk to the environment and human health from C. globosum mycotoxins is estimated to be low.

C. globosum strain ATCC 6205 has useful properties that make it of potential interest for use in additional industrial processes or consumer or commercial products. In the event that these potential consumer, commercial or industrial uses of C. globosum strain ATCC 6205 are realized, the level of environmental and human exposure to these strains could increase. Nevertheless, the risk from foreseeable potential uses of C. globosum strain ATCC 6205 remains low given the low hazard associated with the living organism and the negligible contribution of C. globosum strain ATCC 6205 to the overall burden of mycotoxins in feeds, foods and moisture-damaged buildings, despite potential increases in use.

Risks associated with the potential use of the DSL strain as a biocontrol agent, would be assessed and managed as part of a pesticide registration by Health Canada’s Pest Management Regulatory Agency.

4. Conclusion

Based on the information presented in this screening assessment, it is concluded that C. globosum strain ATCC 6205 is not entering the environment from anthropogenic sources in a quantity or concentration or under conditions that:

- have or may have an immediate or long-term harmful effect in the environment or its biological diversity;
- constitute or may constitute a danger to the environment on which life depends; or
- constitute or may constitute a danger in Canada to human life or health.

Therefore, it is concluded that C. globosum strain ATCC 6205 does not meet the criteria as set out in section 64 of the CEPA.

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Appendices

Appendix A: Growth of C. globosum strain ATCC 6205 in various temperatures

Table A-1: Diameter (in mm) of C. globosum colonies on corn meal agar plates after 24 hours and 5 days, measured by Health Canada scientists

Incubation time	28°C	32°C	37°C	42°C
1 Day	1-3	1-3	1.2	N/A
5 Days	N/A	N/A	N/A	0

"N/A" means no data was available

Table A-2: Growth of C. globosum strain ATCC 6205 at different temperatures in liquid media after 72 hours, measured at an optical density of 500 nanometers by Health Canada scientists

Media	28°C	32°C	37°C	42°C
Sabouraud's dextrose broth (SAB)	0.34	0.30	0.08	0
Yeast extract peptone dextrose (YPD)	1.06	0.60	0.25	0
10% fetal bovine serum (FBS)	0.2	0.23	0.09	0
100% FBS	0.6	0.50	0.17	0
10% sheep serum (SS)	0.04	0.02	0.02	0
100% SS	0.05	0.07	0.09	0
Dulbecco's Modified Eagle's medium (DMEM) with FBS and Glutamine	0.16	0.17	0.13	0

Appendix B: C. globosum strain ATCC 6205 ITS and LSU gene sequence analysis

A 1.9 kb contig representing the rRNA data sequences of ITS1, ITS2, 5.8S ribosomal RNA, and D1/D2 region of LSU were determined by Health Canada's Environmental Health Science and Research Bureau. The derived contig of C. globosum ATCC 6025 rRNA sequences was then compared to both the MicroSeq® Fungal LSU D2 region v 2.0 library and also the Ribosomal Database Project release 11 LSU database (https://rdp.cme.msu.edu/) and the top 10 matches are shown.

Table B-1: Matches to C. globosum strain ATCC 6205 in the MicroSeq® Fungal LSU D2 region v 2.0 library

Match%	Sequence Entry
99.68	Chaetomium globosum CBS=145.38
99.13	Chaetomium brasiliense CBS=493.66
98.40	Chaetomium globosum CBS=149.6
97.54	Chaetomium strumarium CBS=333.67
97.49	Chaetomium atrobrunneum CBS=379.66
97.47	Myceliophthora lutea CBS=145.77
97.44	Chaetomium funicola CBS=794.83
97.22	Chaetomium aureum CBS=515.66
97.21	Chaetomium brasiliense CBS=426.8
97.12	Myceliophthora thermophila CBS=117.65

Table B-2: Ribosomal Database Project release 11 top ten Seqmatch results

Seqmatch score	Number of uniquely occurring oligomers	Sequence name; Culture collection; Accession number
1.000	0564	Chaetomium globosum; Morita Ricci (= IFM 53574); AB292591
1.000	0564	Chaetomium globosum; IFM 40868; AB449672
1.000	0564	Chaetomium globosum; IFM 40869; AB449673
1.000	0564	Chaetomium globosum; IFM 40870; AB449674
1.000	0564	Chaetomium globosum; IFM 40872; AB449675
1.000	0564	Chaetomium globosum; IFM 40873; AB449676
1.000	0564	Chaetomium globosum; IFM 40874; AB449677
1.000	0564	Chaetomium globosum; IFM 40875; AB449678
1.000	0564	Chaetomium globosum; IFM 40876; AB449679
1.000	0564	Chaetomium globosum; IFM 40877; AB449680

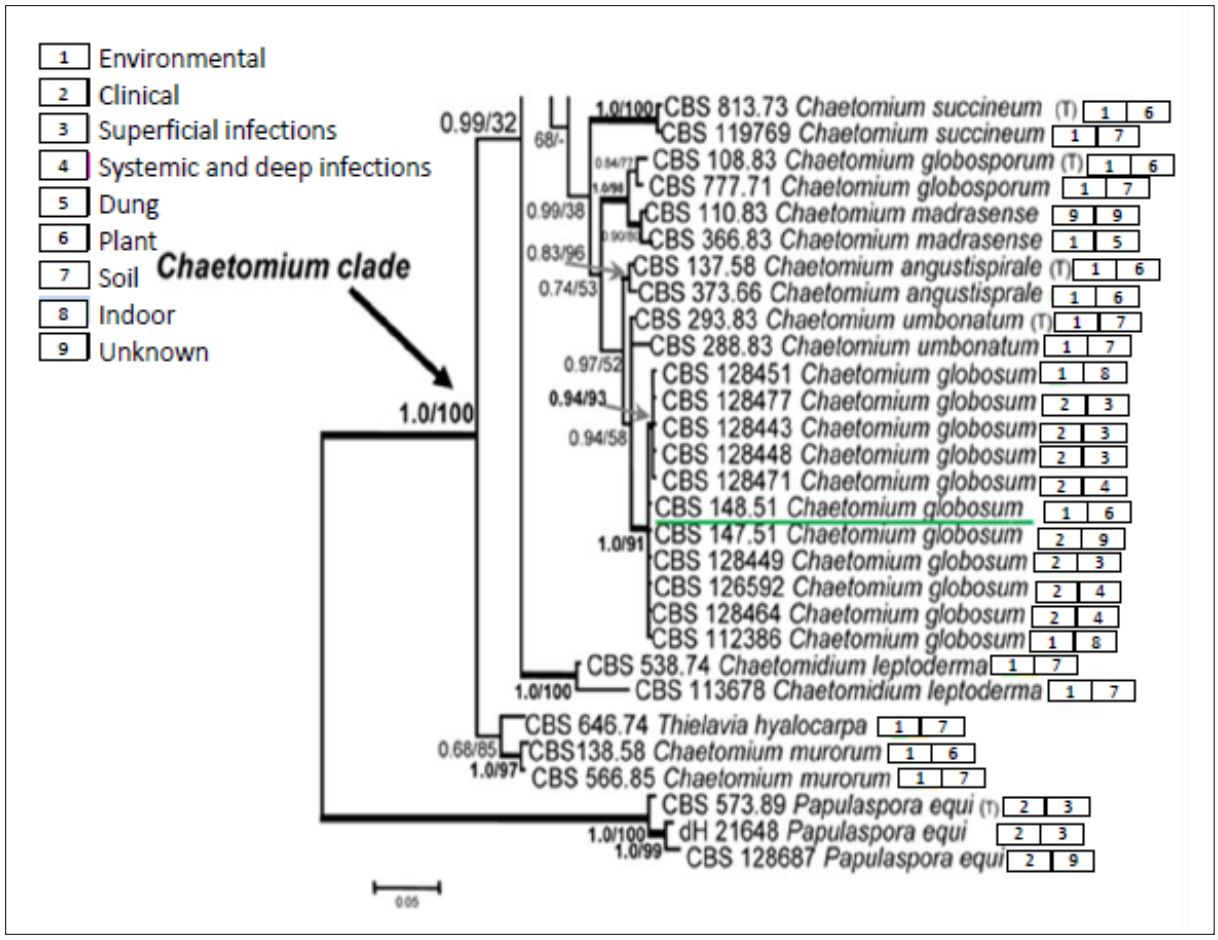

Figure B- 1: Segment of a phylogenetic tree that includes the Chaetomium clade, based on Bayesian and maximum likelihood analysis of the combined ITS/LSU dataset (adapted from de Hoog et al. 2013 with permission, http://journals.plos.org/plosntds/article/figure/image?size=inline&id=10.1371/journal.pntd.0002229.g002).

Appendix C: Carbohydrate consumption of the DSL C. globosum strain ATCC 6205

Table C-1: Carbohydrate utilization used for taxonomic identification of C. globosum strain ATCC 6205, based on the RapID™ YEAST PLUS system

Carbohydrate[a]	Result
Glucose	-
Maltose	-
Sucrose	-
Trehalose	-
Raffinose	-
Fatty Acid Ester	-
p-Nitrophenyl-N-acetyl-β,D-galactosaminide	+
p-Nitrophenyl-α,D-glucoside	-
p-Nitrophenyl-β,D-glucoside	+
o-Nitrophenyl-β,D-galactoside	-
p-Nitrophenyl-α,D-galactoside	+
p-Nitrophenyl-β,D-fucoside	-
p-Nitrophenyl phosphate	+
p-Nitrophenyl phosphorylcholine	-
Urea	+
Proline-β-naphthylamide	+
Histidine β-naphthylamide	+
Leucyl-glycine β-naphthylamide	-

[a] The Thermo Scientific™ RapID™ YEAST PLUS System was used to evaluate sugar consumption of. C. globosum strain ATCC 6205. C. globosum strain ATCC 6205 was inoculated into wells containing various carbon sources and incubated at 28°C. The wells were evaluated after 48 hours.
"+" means that the test result was positive and "-" means that the test result was negative.

Appendix D: Susceptibility of C. globosum to antibiotics, chemicals and irradiation

Table D-1: Susceptibility of C. globosum to irradiation and chemicals as reported in the scientific literature

Name of Compound/ process	Main Usage	Strain name	Activity of compound	Reference
Gamma Irradiation	Disinfectant	Unspecified strain	Complete inhibition by 4756 Grays per hour, for a duration of 1 hour and 3 minutes.	(Michaelsen et al. 2013)
Chlorine dioxide	Fumigant	ATCC 16021	87% and 91% treatment efficacy at 500 ppm and 1000 ppm respectively both following 24 hours of exposure. Both treatments caused 3 log inactivation of the exposed ascospores.	(Wilson et al. 2005)
Chlorine dioxide	Fumigant	ATCC 34507	9000 ppm per hour at 75°C and 75% relative humidity, resulted ≥ 4 log10 reduction in CFU.	US-EPA 2013
Ethylene oxide/CO_2	Fumigant	Unspecified strain	Complete inhibition of growth by the combination of 10% ethylene oxide and 90% CO_2 for 48 hours at 20-22°C.	(Michaelsen et al. 2013)
Pentachlorophenol	Antifungal	Unspecified strain	Inhibited growth at 8-15 ng/L.	Kosak et al. 1979
Pentachlorophenol	Antifungal	ATCC 6205	Inhibited growth at 0.0001-0.00025%	(Howard and Durkin 1073)
Two biosurfactants (sourced from Pseudomonas aeruginosa)	Antifungal	ATCC 6205	High level of inhibition with MIC values of 64 µg/mL and 32 µg/mL.	(Lotfabad et al. 2013)

Triorganotin 5-Nitro-2-furoates	Antifungal	ATCC 6205	4 derivatives tested: complete inhibition by VIb at ≥1 µg/mL and partial inhibition by VIa and VIc at ≥1 µg/mL. Also partial inhibition by VId and VIe at ≥10 µg/mL.	(Kupchik et al. 1982)
N-Substituted N-(triphenylstanny1)cyanamides (i.e. series IV) and their triethylammonium chloride complexes (i.e. series V and VI)	Antifungal	ATCC 6205	17 derivatives tested: complete inhibition by 8 compounds (IVa, IVe, IVi, Vb,Vc,Vd,Vg and a single VI comound tested) at ≥100 µg/mL and at ≥10 µg/mL by Vf.	(Kupchik et al. 1980)
Novel bis-quaternary ammonium compounds	Antifungal	FERM S-11	MIC values of 3.1±0.0, 6.5, 008.3 ± 02.9 and 10.0±2.9 µM for the four compounds tested.	(Kourai et al. 2006)
Gramoxone W and Roundup (Paraquat, active ingredient in both)	Herbicides	Unspecified strain	Gramoxone W: complete inhibition of growth by at 80 ppm of paraquat. Roundup: fungus growth with altered colony morphology seen even at the higher concentration of 640 ppm of the active ingredient (glyphosate).	(Grossbard and Harris 1977)

Lithium chloride	Inhibition of fungal growth in the microbiologic al media	ATCC 6205	Highly tolerant. Growth of more than 80% of control following 2 weeks of exposure to LiCl at concentrations of 1.5, 3.0, or 6.0 g/L in malt agar. Some adaptation was evident as rate of growth increased over time.	(Lotfabad et al. 2013; Richter et al. 2008)
Silver chloride	Antimicrobial used as textile preservative	ATCC 6205	Effective inhibition of growth at concentrations of >100 ppm in the impregnated fabric.	(Tomšič et al. 2009)
Calcium benzoate, potassium sorbate, zinc salicylate and zinc benzoate	Antimicrobial used as food preservatives	Unspecified strain	At the concentration of 0.03% (w/v) in the growth media and as coatings for painted glass all showed inhibitory activity, although the highest efficacy was reported for zinc salicylate and zinc benzoate.	(Bellotti et al. 2013)
Esters of para-hydroxy-benzoic acid	Preservative used in in pharm-aceuticals, cosmetics, foods, and industrial products	ATCC 6205	Mainly fungistatic. MIC values: 0.05% for the methyl ester, 0.025% for ethyl ester, 0.0063% for propyl ester and <0.0032 for butyl ester.	(Aalto et al.1953)
Peracetic acid	Disinfectant/ preservative for food processing machinery and environment	IFM 57189	Highly resistant, D-value of 1998 seconds (i.e. causing one log reduction) following exposure to 1000 ppm (±5%) at 40°C.	(Nakayama et al. 2013)
Acriflavin-HCl; Basic Blue 9	Industrial dyes	ATCC 6205	Variable growth at 1:100 dilution. Variable growth at 1:1000 dilution.	(Thakur and Fung 1995)

Basic Green 1; Basic Green 4	Industrial dyes	ATCC 6205	Growth inhibition at 1:1000 dilution.	(Thakur and Fung 1995)
Basic Violet 1; Basic Violet 3	Industrial dyes	ATCC 6205	Growth inhibition at 1:1000 dilution.	(Thakur and Fung 1995)
Basic Violet 4	Industrial dyes	ATCC 6205	Variable growth at 1:10000 dilution. Growth inhibition at 1:1000 dilution.	(Thakur and Fung 1995)
Basic violet 14; Basic yellow 2	Industrial dyes	ATCC 6205	Growth not inhibited at any of the dilutions tested.	(Thakur and Fung 1995)
Acid dyes; Disperse dyes	Industrial dyes	ATCC 6205	Growth not inhibited at any of the dilutions tested.	(Thakur and Fung 1995)
Eucalyptus urophylla, Eucalyptus grandis and Eucalyptus citriodora	Essential oils	ATCC 6205	Full growth suppression at 10 mg essential oil per culture disc until the end of experiment i.e. day 21.	(Su et al. 2006)
Eucalyptus camedulensis	Essential oils	ATCC 6205	Resistant to the oil.	(Su et al. 2006)
Cinnamomum zeylanicum	Essential oils	ATCC 6205	Demonstrated some sensitivity to the oil with a MIC value of 63 µL/mL.	(Moreira et al. 2007)
β-pinene (sourced from C. zeylanicum)	Phyto-chemical	ATCC 6205	Resistant to all assayed concentrations of the isolate.	(Moreira et al. 2007)

Table D-2: MIC range (µg/mL) of antifungals based on broth dilution assay against 8 clinical and 8 saprobic isolates morphologically identified by the authors as C. globosum, from Guarro et al. 1995

Antifungal agent	Clinical isolates	Saprobic isolates
Amphotericin B[a]	0.58 - 1.16	1.16 - 2.31
5-Fluorocytosine[a]	> 645.5	> 645.5
Fluconazole[a]	40 - 160	80 - 160
Itraconazole[b]	0.035 - 0.3	0.035 - 0.3
Ketoconazole[a]	0.8 - 1.6	1.6
Miconazole[a]	0.075	0.75 - 0.15

[a]Tested at 48 hours
[b] Tested at 72 hours

Table D-3: MIC (µg/mL) of antifungal agents against clinical strains identified as C. globosum in the scientific literature

Antifungal agent	Hattori et al. 2000[a]	Yu et al. 2006[b]	Naidu et al. 1991[b]	Sugiyama et al. 2008[b]
Amphotericin B	2	4	resistant	4
Itraconazole	0.25	0.5	N/A	0.5
Miconazole	0.5	N/A	N/A	1.0
Fluconazole	64	>64	N/A	16.0
Ketoconazole	N/A	N/A	3	0.25
Micafungin	N/A	N/A	N/A	16.0
Oxicomazole	N/A	N/A	0.3	N/A
Amorolfine	N/A	N/A	10	N/A
5-fluorocytosine	64	v	100	N/A

" N/A" means not available
" v" means variable
[a] Method not disclosed
[b] Agar dilution method

Table D-4: MIC (µg/mL) of C. globosum strain ATCC 6205 based on the broth dilution assay measured by Health Canada scientists

Antimicrobial	MIC[a] (µg/mL)	Results
Amphotericin B	>24	-
Amphotericin B plus 5-Fluorocytosine	>24	-
5-Fluorocytosine	>24	-
Clotrimazole	6	+
Griseofulvin	>24	-
Intraconazole	1.5	NR
Isoconazole,	0.5 ± 0.2	+
Micafungin	0.37	NR
Nystatin	>24	-
Terbinafine	6	+

[a] Broth dilution assay was used to determine the MIC values and was modified from the method discussed in Seligy and Rancourt 1997. Values correspond to the MIC (µg/mL) for C. globosum strain ATCC 6205 grown in the presence of antibiotic for 96 hours at room temperature. MIC values represent the lowest antibiotic concentration (µg/ml) that prevents any discernible growth for the incubation period.
effective: "+" , ineffective":- ", effective and ineffective relate to the relative efficacy of the antifungal agent and does not necessarily reflect clinical effectiveness of that drug.
NR, Not reported

Appendix E: Toxins and secondary metabolites produced by C. globosum strain ATCC 6205

Table E-1: Chaetoglobosin and azaphilones produced by C. globosum strain ATCC 6205 in mg/L/ga measured by Carlton University research scientists

Strain	Chaeto-globosin A	Chaeto-globosin C	Chaeto-globosin F	Chaeto-mugilin D	Chaeto-viridin A
ATCC 6205	0.99 ± 0.25	0.38 ± 0.12	2.12 ± 0.14	0.11 ± 0.12	0.04 ± 0.03
DAOM 240349[b]	21.98 ±3.20	2.50 ± 0.36	4.81 ± 0.20	2.38 ± 0.36	0.61 ± 0.15
DAOM 240357[b]	2.70 ± 1.38	0.70 ± 0.25	3.30 ± 1.67	2.08 ± 0.25	0.44 ± 0.06

[a]Quantities reported as mg/L/g dry mycelium
[b]Positive control strains Canadian strains of C. globosum deposited in DAOM of known toxigenic potential

Table 3: List of toxins and secondary metabolites produced by C. globosum in the scientific literature

Toxins	Actions
Chaetoglobosins (including cytochalasans)	• Produced by some strains of C. globosum (Straus 2011; Ding et al. 2006). • Multiple forms: A, B, C, D, E, F, F_a, $F_{ex,}$ G, J, Q, R, T, U, V, V_b, W, X, Y (Ding et al. 2006; Jiao et al. 2004; Li et al. 2013; Sekita et al. 1973, 1976 and 1982; Wang et al. 2012; Xue et al. 2012; Zhang et al. 2010; Zheng et al. 2014) and penochalasin A (Ding et al. 2006). • Forms A and C showed in vitro antibacterial (Jiao 2004; McMullin et al. 2013), antifungal (Zhang et al. 2013) and nematicidal (Hu et al. 2013; Qin et al. 2009) activities. • Form A showed phytotoxic activity against radish seedlings at 50 ppm (Li et al. 2014). • Relatively low levels of chaetoglobosins A and C have been shown to be lethal to various human cancer cell lines (Li et al. 2014; Sekita et al. 1982, respectively). • Chaetoglobosin A (Ohtsubo et al. 1978): o LD_{50}: 6.5 mg/kg and 17.8 mg/kg in male and female mice (subcutaneous) respectively. • Form F_{ex} showed in vitro anti-inflammatory effects when tested against both human and murine macrophages (Dou et al. 2011). • Penochalasin A displayed moderate cytotoxicity to human cancer cells (KB) with an IC_{50} of 48.0 µM (Ding et al., 2006). No LD_{50} or information on toxicity available. • C. globosum strain ATCC 6205 produces chaetoglobosins A, C and F (see Table E-1 in Appendix E).

Toxins	Actions
Chaetomugilins	• Produced by 25 Canadian strains of C. globosum (see McMullin et al. 2013 for listing), OUPS-T106B-6 (Yasuhide et al. 2008; Yamada et al. 2011). • Multiple forms: A, B, C, D, E, F (McMullin et al. 2013; Yasuhide et al. 2008), P, Q and R (Yamada et al. 2011), 11-Epi-chaetomugulin I (Yamada et al. 2011) and seco-chaeto-mugulin D (Yamada et al. 2009). • Forms A, B, C, D, E, F and P are cytotoxic against human (H) and murine (M) cancer lines: o Forms C and F for HepG2 (H) cells: significant activity, IC_{50} values of 2.7 and 1.3 µM, respectively (Yasuhide et al. 2008). o Forms C and F for P388 (M) cells: significant activity, IC_{50} values of 3.6 and 3.3 µM, respectively (Yasuhide et al. 2008). o Form F showed highest selective growth inhibition of disease oriented panel of 39 human cancer cell lines (Yasuhide et al. 2008). o Form P for HL-60 (H), KB (H), P388 (M) and L1210 (M): significant activity, IC_{50} values of 1.2, 1.8, 0.7 and 1.5 pM, respectively (Yamada et al. 2011). • Form 11-Epi-chaetomugulin I showed significant cytotoxicity to all human and murine cancer cell lines tested: HL-60 (H), KB (H), P388 (M) and L1210 (M) with an IC_{50} of 1.0, 1.2, 0.7 and 1.6 pM respectively (Yamada et al. 2011). • Form seco-chaeto-mugulin D displayed moderate cytotoxicity to all human and murine cancer cell lines tested: HL-60 (H), KB (H), P388 (M) and L1210 (M) with an IC_{50} of 47.2, 47.2, 38.6 and 53.6 µM respectively (Yamada et al. 2009). • No LD_{50} information available. • C. globosum strain ATCC 6205 produces chaetomugulin D (see Table E-1 in Appendix E).
Chaetoviridins	• Produced by C. globosum F0142 (Park et al. 2005) • Multiple forms: A, B, C, D (Takahashi et al. 1990), J and K (Youn et al., 2015). • Reported antifungal activities for forms A and B (Park et al. 2005). • No LD_{50} or information on toxicity available. C. globosum strain ATCC 6205 produces chaetoviridin A (see Table E-1 in Appendix E).

Toxins	Actions
Chaetomugilides	• Produced by C. globosum strains TY1 and OUPS-T106B-6 (Li et al. 2013; Yasuhide et al. 2008). • Multiple forms: A, B and C (Li et al. 2013). • Forms A, B, are cytotoxic against human cancer cell lines (HepG2) and (Li et al. 2013): o Form A: significant activity, IC_{50} value of 1.7 µM. o Forms B and C: moderate activity, IC_{50} values ranging of 19.8 - 53.4 µM. • No LD_{50} or information on toxicity available. • No indication if C. globosum strain ATCC 6205 produces chaetomugilides.
Cytoglobosins	• Produced by C. globosum strains QEN-14 (Cui et al. 2014) and No.64-5-8-2 (Zheng et al. 2014). • Multiple forms: A, B, C, D, E, F, F_{ex} and G (Cui et al. 2014). • Forms C and D are cytotoxic against human cancer cell lines: o Form C for A-549 and HCT-116: IC_{50} values of 2.26 µM (Cui et al. 2014) and 11.32 ± 1.00 µM (Zheng et al. 2014), respectively. o Form D for A-549:IC_{50} value of 2.55 µM (Cui et al. 2010). • No LD_{50} or information on toxicity available. No indication if C. globosum strain ATCC 6205 produces cytoglobosins.
Chaetomin	• Produced by some strains of C. globosum (Brewer et al. 1966; Brewer et al. 1972). • Displayed inhibitory activity against Bacillus subtilis with a MIC value of 0.08 µg/mL (Brewer et al. 1966). • Reported antifungal activity against P. ultimum, comparable to the positive control at EC_{50} and MIC values of 0.5 and 2.5 mg active ingredient /L, respectively (Di Pietro et al. 1992). • Cytotoxic to human cancer cells (HeLa) at 0.02 µg/mL (Brewer et al. 1972). • LD_{50}: 5 mg/kg in lambs (intraperitoneal injection); 75 mg/kg in rats and 30 mg/kg in turkeys (both oral) (Brewer et al. 1972). • No indication if C. globosum strain ATCC 6205 produces chaetomin.
Flavipin	• Produced by C. globosum CDW7 (Ye et al. 2013). • Displayed significant antifungal activity against F. graminearum with an IC_{50} value of 0.73 µg/mL (reviewed in Ye et al. 2013).

Toxins	Actions
	• A potent antioxidant as was shown in both in vitro and in vivo assays (Ye et al. 2013). • No LD_{50} or information on toxicity available. • No indication if C. globosum strain ATCC 6205 produces flavipin.
Protochaeto-globosins	• Produced by C. globosum CANU N60 (Jiao et al. 2004). • Two forms: I and II (Jiao et al. 2004). • Both showed antifungal activities at 30 µg/disk against T. mentagrophytes with a zone of inhibition of 2 mm (Jiao et al. 2004). • Both displayed significant cytotoxicity to murine cancer cells (P388) with an IC_{50} of 3.99 µg/mL (Jiao et al. 2004). • No LD_{50} or information on toxicity available. • No indication if C. globosum strain ATCC 6205 produces protochaeto-globosins.
20-dihydro-chaeto-globosin A	• Produced by C. globosum (unspecified strain) (Li et al. 2014)(Yamada et al. 2009) • Displayed high cytotoxicity to all human cancer cell line tested: HTC116, with an IC_{50} of 8.44 µM (Li et al. 2014) • No LD_{50} or information on toxicity available. • No indication if C. globosum strain ATCC 6205 produces 20-dihydro-chaetoglobosin A.
N-2-butyric-azochaetoviridin E	• Produced by C. globosum DAOM 240359 (McMullin et al. 2013) • Displayed significant antibacterial activities at 20 µM against Pseudomonas putida and Bacillus subtilis (McMullin et al. 2013). • Displayed significant antifungal activity at 200 µM against Saccharomyces cerevisiae(McMullin et al. 2013) • No LD_{50} or information on toxicity available. • No indication if C. globosum strain ATCC 6205 produces N-2-butyric-azochaetoviridin E.