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Draft Assessment

Titanium-containing Substances Group

Environment and Climate Change Canada
Health Canada

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Canada

Synopsis

Pursuant to section 68 of the *Canadian Environmental Protection Act, 1999* (CEPA), the Minister of the Environment and the Minister of Health have conducted an assessment of 13 substances referred to collectively as the Titanium-containing Substances Group. The Chemical Abstracts Service Registry Numbers (CAS RN[1]), *Domestic Substances List* (DSL) names and common names of these substances are listed in the table below.

Substances in the Titanium-containing Substances Group

CAS RN[1]	DSL name	Common name
546-68-9	2-Propanol, titanium(4+) salt	Titanium tetraisopropanolate
1070-10-6	1-Hexanol, 2-ethyl-, titanium(4+) salt	Titanium tetrakis(2-ethylhexanolate)
1317-80-2	Rutile (TiO_2)	Rutile (TiO_2)
1344-54-3	Titanium oxide (Ti_2O_3)	Dititanium trioxide
13463-67-7	Titanium oxide (TiO_2)	Titanium dioxide
5593-70-4	1-Butanol, titanium(4+) salt	Titanium tetrabutanolate
7550-45-0	Titanium tetrachloride	Titanium tetrachloride
7705-07-9	Titanium chloride ($TiCl_3$)	Titanium trichloride
12047-27-7	Titanate (TiO_3^{2-}), barium (1:1)	Barium titanate (IV)
12060-59-2	Titanate (TiO_3^{2-}), strontium (1:1)	Strontium titanium oxide
13825-74-6	Titanium, oxo[sulfato(2-)-O,O']-	Titanium oxide sulphate
16919-27-0	Titanate(2-), hexafluoro-, dipotassium, (OC-6-11)-	Dipotassium hexafluorotitanate
20338-08-3	Titanium hydroxide ($Ti(OH)_4$), (T-4)-	Tetrahydroxytitanium

Abbreviations: CAS RN, Chemical Abstracts Service Registry Number; DSL, *Domestic Substances List*
[1] Substance was identified as a priority for assessment as it met categorization criteria under subsection 73(1) of CEPA.

The potential for cumulative effects was considered in this assessment by examining cumulative exposures from the broader moiety of titanium. Titanium is a naturally occurring metal that is present in the environment predominantly as titanium oxides.

According to information submitted in response to a CEPA section 71 survey, 10 of the 11 surveyed titanium-containing substances in this group were manufactured or imported above the reporting threshold of 100 kg. Activities and uses involving these substances reported in Canada include metal mining and refining, processing intermediates, laboratory substances, fabric and textiles, adhesives and sealants, paints and coatings, water repellants, apparel and footwear care, automotive care, cleaning and furnishing care, building materials, floor coverings, food packaging materials and electronics. In addition, some of the substances in the Titanium-containing Substances Group are permitted food additives. They are present in a range of products available to consumers including self-care products (that is, cosmetics, natural health products, and non-prescription drugs), pest control products, do-it-yourself (DIY) products (for example, lubricants and greases, home maintenance products), cleaning products, plastics and rubber products, paper products, inks and printing supplies, toys and arts and crafts products.

The ecological risks of the 13 titanium-containing substances were characterized using the Ecological Risk Classification of Inorganic Substances (ERC-I). ERC-I is a risk-based approach that employs multiple metrics considering both hazard and exposure, with weighted consideration of multiple lines of evidence for determining risk classification. Hazard characterization in ERC-I included a survey of published predicted no-effect concentrations (PNECs) and water quality guidelines, or the derivation of new PNEC values when required. Exposure profiling considered two approaches: predictive modelling using a generic near-field exposure model for each substance, and an analysis of measured concentrations collected by federal and provincial water quality monitoring programs using these concentrations as a conservative indicator of exposure for individual substances. Measured and modelled predicted environmental concentrations were compared to PNECs, and multiple statistical metrics were computed and compared to decision criteria to classify the potential to cause harm to the environment. Based on the outcome of the ERC-I analysis, the 13 titanium-containing substances are considered unlikely to be causing ecological harm.

Considering all available lines of evidence presented in this draft assessment, there is low risk of harm to the environment from the 13 substances in the Titanium-containing Substances Group. It is proposed to conclude that the 13 substances in the Titanium-containing Substances Group do not meet the criteria under paragraphs 64(*a*) or (*b*) of CEPA as they are 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.

Canadians may be exposed to substances in the Titanium-containing Substances Group in air, drinking water, food, soil, house dust, as well as through the use of products available to consumers. Food is a major contributing source of exposure to titanium for the general population. In the absence of substance-specific exposure data, measured and modelled concentrations of titanium were used as surrogate data.

Children between ages 4 and 13 years old had the highest estimated exposure to titanium from environmental media, food and drinking water. Systemic exposure to substances in the Titanium-containing Substances Group by the general population of Canada was characterized using nationally representative titanium whole blood biomonitoring data from the Canadian Health Measures Survey (CHMS) cycle 2 (2009–2011). Total titanium concentrations in whole blood provide a biologically relevant, integrated measure of systemic exposure resulting from multiple routes (for example, oral ingestion, dermal contact and inhalation) and multiple sources (for example, natural and anthropogenic, environmental media, food, and frequent- or daily-use products). Titanium was not detected in the whole blood samples obtained from CHMS cycle 2 (2009-2011) at or above the limit of detection of 10 micrograms per litre (µg/L) in 99.97% of the Canadian population aged 3 years to 79 years.

A no-observed-adverse-effects level (NOAEL) of 623 milligrams of titanium per kilogram of body weight per day (1 000 milligrams of titanium dioxide per kilogram of body weight per day) was considered as the critical point of departure for risk characterization of systemic exposure. The NOAEL is based on lack of effects in multiple endpoints, including reproductive and developmental effects, developmental neurotoxicity and the formation of aberrant crypt foci in the colon in an extended one-generation reproductive toxicity (EOGRT) study in rats exposed to food-grade titanium dioxide via diet. A biomonitoring equivalent (BE) of 65 µg/L was derived for the NOAEL from the EOGRT study. Titanium blood concentrations from the CHMS based on the limit of detection of 10 µg/L were below the BE of 65 µg/L and considered to be low enough to account for uncertainties in the health effects and exposure data used to characterize risk. Therefore, the substances in the Titanium-containing Substances Group are considered to be of low concern to the health of the general population in Canada at current levels of systemic exposure.

For inhalation exposure, non-cancer portal-of-entry effects in the respiratory system (that is, tracheitis, rhinitis with squamous metaplasia of the anterior nasal cavity, alveolar cell hyperplasia and broncho/bronchiolar pneumonia) associated with titanium dioxide exposure in rats were identified as the critical health effect for chronic inhalation exposure. These portal-of-entry effects likely occurred from direct interaction of the substance on the lungs following chronic inhalation exposure. Lung tumours were noted in 2-year inhalation bioassays conducted in experimental animals. These lung tumours were not considered to be relevant to the general population as tumours only occurred at doses that caused lung overload in experimental animals. Inhalation exposures from ambient air and the use of products available to consumers were quantified. The resulting margins of exposure estimated for inhalation exposure were considered adequate to address uncertainties in the available health effects and exposure data used to characterize risk.

The human health assessment took into consideration those groups of individuals within the Canadian population who, due to greater susceptibility or greater exposure, may be more vulnerable to experience adverse health effects from exposure to substances. The

health effects assessment took into consideration the potential for differences in kinetic behavior or increased susceptibility to titanium-induced health effects based on life-stage (for example, developing fetus), age and sex. Exposure of infants and children, certain Indigenous populations, pregnant people, and people living in the vicinity of industrial point sources were considered in the human health assessment. Children were found to have higher exposure to titanium than adults from environmental media, food and drinking water. Indigenous peoples, including pregnant women, from Northern Saskatchewan, were found to have a lower dietary intake of titanium compared to the general population.

Considering all of the information presented in this draft assessment, it is proposed to conclude that the 13 substances in the Titanium-containing Substances Group do not meet the criteria under paragraph 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 in Canada to human life or health.

It is therefore proposed to conclude that the 13 substances in the Titanium-containing Substances Group do not meet any of the criteria set out in section 64 of CEPA.

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1. Introduction

Pursuant to section 68 of the *Canadian Environmental Protection Act, 1999* (CEPA) (Canada 1999), the Minister of the Environment and the Minister of Health have conducted an assessment of 13 substances referred to collectively as the Titanium-containing Substances Group to determine whether these substances present or may present a risk to the environment or to human health. The substances in this group were identified as priorities for assessment as they met categorization criteria as described in ECCC, HC (modified 2017).

This group does not include all titanium-containing substances on the *Domestic Substances List* (DSL). This assessment only considers effects associated with titanium substances and does not address other elements or moieties that may be present in the substances in the Group (such as barium, fluoride, strontium, and organic-metal salts). Some of these other elements or moieties have been addressed through previous assessments via other initiatives of the Chemicals Management Plan (CMP). Nanomaterials[2] containing titanium (particles 1 to 100 nm) that may be present in environmental media, food or products are not explicitly considered in the exposure scenarios of this assessment, but measured concentrations of titanium in the environment or human biomonitoring data could include nanoscale titanium from these sources. Similarly, this assessment does not explicitly consider ecological or health effects associated with nanomaterials containing titanium. Nanomaterials can have different physicochemical and toxicological properties, as well as use patterns, compared to larger materials with the same chemical composition (also known as bulk materials). The Government of Canada has committed to addressing nanoscale forms of substances on the DSL, including nanoscale titanium dioxide, which will be considered in a future assessment (Health Canada [modified 2022a]; ECCC, HC 2022).

[2] According to the Health Canada working definition the term “nanomaterial” includes any manufactured substance or product and any component material, ingredient, device or structure at or within the nanoscale in at least one external dimension, or has internal or surface structure at the nanoscale, or; is smaller or larger than nanoscale in all dimensions and exhibits one or more nanoscale properties/phenomena (Health Canada [modified 2011]). For the purpose of this definition, “nanoscale” means 1 to 100 nanometers, inclusive. “Nanoscale properties/phenomena” means properties which are attributable to size and their effects; these properties are distinguishable from the chemical or physical properties of individual atoms, individual molecules and bulk material. The term “manufactured” includes engineering processes and the control of matter.

The ecological risks of the 13 substances in the Titanium-containing Substances Group were characterized using the Ecological Risk Classification of Inorganic Substances (ERC-I) (ECCC 2020). ERC-I is a risk-based approach that employs multiple metrics considering both hazard and exposure, with weighted consideration of multiple lines of evidence for determining risk classification. Hazard characterization in ERC-I included a survey of published predicted no-effect concentrations (PNECs) and water quality guidelines, or the derivation of a new PNEC value when required. Exposure profiling considered two approaches: predictive modelling using a generic near-field exposure model for each substance and an analysis of measured concentrations collected by federal and provincial water quality monitoring programs using metal concentrations as a conservative indicator of exposure for individual substances. Measured and modelled predicted environmental concentrations (PECs) were compared to PNECs, and multiple statistical metrics were computed and compared to decision criteria to classify the potential for causing harm to the environment.

The human health risks of systemic exposure to substances in the Titanium-containing Substances Group were characterized using the Biomonitoring-based Approach 2 (Health Canada 2016a), which compares human biomonitoring data (exposure) against biomonitoring guidance values (health effects), such as biomonitoring equivalents, to assess if substances are of low concern for human health. A route specific approach was used to characterize portal of entry effects from the inhalation route of exposure for substances in the Titanium-containing Substances Group.

This draft assessment considers information on chemical hazards, uses and exposures, including additional information submitted by stakeholders. Relevant data were identified up to June 2022. Empirical data from critical studies as well as results from models were used to reach proposed conclusions. When available and relevant, the information presented in assessments from other jurisdictions was considered.

This draft assessment was prepared by staff in the CEPA Risk Assessment Program at Health Canada and Environment and Climate Change Canada and incorporates input from other programs within these departments. The human health portion of this assessment has undergone external review and consultation. Comments on the technical portions relevant to human health were received from T. Lopez, J. Flippin and J. Garey from Tetra Tech. The ecological portion of this assessment is based on the ERC-I Science Approach Document (published May 12, 2018), which was externally peer-reviewed and subject to a 60-day public comment period. The human health portion of this assessment is based in part on the Biomonitoring-based Approach 2 Science Approach Document (published December 9, 2016) which was subject to a 60-day public comment period. While external comments were taken into consideration, the final content and outcome of this assessment remain the responsibility of Health Canada and Environment and Climate Change Canada.

Assessments focus on information critical to determining whether substances meet the criteria as set out in section 64 of CEPA by considering scientific information, including

information, if available, on subpopulations who may have greater susceptibility or greater exposure, vulnerable environments and cumulative effects[3], and by incorporating a weight-of-evidence approach and precaution[4]. This draft assessment presents the critical information and considerations on which the proposed conclusion is based.

2. Identity of substances

The Chemical Abstracts Service Registry Numbers (CAS RNs[5]), *Domestic Substances List* (DSL) names and common names for the 13 substances in the Titanium-containing Substances Group are presented in Table 2-1.

Table 2-1. Substance identities

CAS RN	DSL name	Common name
546-68-9	2-Propanol, titanium(4+) salt	Titanium tetraisopropanolate
1070-10-6	1-Hexanol, 2-ethyl-, titanium(4+) salt	Titanium tetrakis(2-ethylhexanolate)
1317-80-2	Rutile (TiO_2)	Rutile (TiO_2)
1344-54-3	Titanium oxide (Ti_2O_3)	Dititanium trioxide
13463-67-7	Titanium oxide (TiO_2)	Titanium dioxide
5593-70-4	1-Butanol, titanium(4+) salt	Titanium tetrabutanolate
7550-45-0	Titanium tetrachloride	Titanium tetrachloride
7705-07-9	Titanium chloride ($TiCl_3$)	Titanium trichloride

[3] The consideration of cumulative effects under CEPA may involve an analysis, characterization and possible quantification of the combined risks to health or the environment from exposure to multiple chemicals.

[4] A determination of whether one or more of the 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 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 *Hazardous Products Regulations*, which are part of the regulatory framework for the Workplace Hazardous Materials Information System for products intended for workplace use. Similarly, a conclusion based on the criteria contained in section 64 of CEPA does not preclude actions being taken under other sections of CEPA or other acts.

[5] The Chemical Abstracts Service Registry Number (CAS RN) 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.

CAS RN	DSL name	Common name
12047-27-7	Titanate (TiO_3^{2-}), barium (1:1)	Barium titanate (IV)
12060-59-2	Titanate (TiO_3^{2-}), strontium (1:1)	Strontium titanium oxide
13825-74-6	Titanium, oxo[sulfato(2-)-O,O']-	Titanium oxide sulphate
16919-27-0	Titanate(2-), hexafluoro-, dipotassium, (OC-6-11)-	Dipotassium hexafluorotitanate
20338-08-3	Titanium hydroxide ($Ti(OH)_4$), (T-4)-	Tetrahydroxytitanium

Abbreviations: CAS RN, Chemical Abstracts Service Registry Number; DSL, *Domestic Substances List.*

3. Sources and uses

3.1 Natural sources

Titanium is a naturally occurring element. It is the ninth most abundant element in the earth's crust and is found in many rocks and sediments globally (Woodruff et al. 2017). The mean concentration of titanium in the soil is estimated at 0.33 weight percent globally (Woodruff et al. 2017). Titanium is not found naturally as a pure metal because it has a strong affinity for oxygen and typically forms oxide minerals (Woodruff et al. 2017; USGS 2018). Titanium minerals and materials of economic importance include ilmenite ($FeTiO_3$), titanium dioxide polymorphs rutile, anatase and brookite. Less common titanium minerals include pseudobrookite (Fe_2TiO_5), perovskite ($CaTiO_3$), geikielite ($(Mg,Fe)TiO_3$), pyrophanite ($MnTiO_3$), and titanite or sphene ($CaTiSiO_5$). The titanium content in titanium minerals ranges between approximately 2% to 20% titanium.

3.2 Anthropogenic sources

3.2.1 Titanium production

Titanium is sourced from mineral deposits, extracted from the earth by the metal mining industry and further processed and refined by the metal smelting and refining industry. Canada was the third largest producer of ilmenite globally in 2019, producing 9.9% of total global ilmenite (USGS 2020). There is one open cast titanium mine in Canada, located near Havre-Saint-Pierre Québec, which produced 2 100 000 tonnes of magmatic ilmenite in 2019 (Rio Tinto 2019a). The ilmenite ore is processed into titanium slag, used to produce titanium dioxide products, at a nearby associated metallurgical complex in Sorel-Tracy, Québec (Rio Tinto 2019b). The metallurgical complex in Sorel-Tracy, Québec produced 800 000 tonnes of titanium slag in 2019. The titanium industry is currently limited to a few facilities in Canada but has the potential to expand based on new technologies to extract titanium from heavy mineral sands and non-conventional ore minerals as well as the potential for increased global demand for titanium metal and titanium dioxide (USGS 2013; Woodruff et al. 2017).

3.2.2 Manufacture and imports

Eleven out of the 13 substances in the Titanium-containing Substances Group were included in a survey issued pursuant to section 71 of CEPA (Canada 2012). Table 3-1 presents a summary of the information reported on the total manufacture and total import quantities for these substances in Canada for the 2011 reporting year. Rutile titanium dioxide (CAS RN 1317-80-2) and titanium dioxide (CAS RN 13463-67-7) were not included in the survey because they were already known to be imported in high quantities in Canada. Data for relevant harmonized system (HS) codes[6] indicate approximately 10 000 000 to 100 000 000 kg were imported annually between 2010 and 2013 (CIMTWA [modified 2022b]).

Table 3-1. Summary of information on Canadian manufacturing and imports of 11 titanium-containing substances submitted in response to a CEPA section 71 survey (Environment Canada 2013)

DSL name	CAS RN	Total manufacture[a] (kg)	Total imports[a] (kg)
2-Propanol, titanium(4++) salt	546-68-9	NR	1 000 to 10 000
1-Hexanol, 2-ethyl-, titanium(4+) salt	1070-10-6	100 to 1 000	1 000 to 10 000
Titanium oxide (Ti_2O_3)	1344-54-3	NR	10 000 to 100 000
1-Butanol, titanium(4+) salt	5593-70-4	NR	1 000 to 10 000
Titanium tetrachloride	7550-45-0	Over 10 000 000	10 000 to 100 000
Titanium chloride ($TiCl_3$)	7705-07-9	1 000 to 10 000	1 000 to 10 000
Titanate (TiO_3^{2-}) barium (1:1)	12047-27-7	NR	1 000 to10 000

[6] Relevant HS 10 codes considered in ERC-I (relevant years) include: 2823.00.1000 (2010, 2011), 2823.00.0010 (2012, 2013), 2823.00.9000 (2010, 2011), 2823.00.0090 (2012, 2013), 2827.39.9010 (2010, 2011), 2827.39.0030 (2012, 2013), 2827.39.1020 (2010, 2011), 3206.11.1000 (2010, 2011, 2012, 2013), 3206.11.9010 (2012, 2013), and 3206.11.9020 (2012, 2013), 3206.19.9090 (2012, 2013). These HS codes have been revised in subsequent years and therefore are different than data included in Table 3-2.

DSL name	CAS RN	Total manufacture[a] (kg)	Total imports[a] (kg)
Titanate (TiO_3^{2-}), strontium (1:1)	12060-59-2	NR	NR
Titanium, oxo[sulfato(2-)-O,O']-	13825-74-6	100 000 to 1 000 000	NR
Titanate(2-), hexafluror-, dipotassium, (OC-6-11)-	16919-27-0	NR	100 to 1 000
Titanium hydroxide ($Ti(OH)_4$), (T-4)-	20338-08-3	NR	100 to 1 000

Abbreviations: CAS RN, Chemical Abstracts Service Registry Number; DSL, *Domestic Substances List;* NR, Not reported above reporting threshold of 100 kg

[a] Values reflect quantities reported in response to the surveys issued pursuant to section 71 of CEPA (Environment Canada 2013). See surveys for specific inclusions and exclusions (schedules 2 and 3).

Import and export quantities from the Canadian International Merchandise Trade Web Application (CIMTWA) were considered to identify quantities imported and exported in Canada in recent years. Import and export quantities of three titanium containing HS 6 codes relevant to the 13 titanium-containing substances in this assessment (listed in Table 3-2) from 2017 to 2021 were considered (CIMTWA [modified 2022a]). The three relevant HS 6 codes include titanium oxides and titanium pigments, trade commodities that may be sources of the substances in the Titanium-containing Substances Group. During 2017 to 2021, Canada imported between 6 961 041 to 82 402 444 kg of relevant titanium commodities per year and exported 6 842 492 to 110 676 653 kg of relevant titanium commodities per year (Table 3-2) (CIMTWA [modified 2022a]).

Table 3-2. Summary of annual titanium-containing commodities imported and exported in Canada from 2017 to 2021 (CIMTWA [modified 2022a])

HS 6 code name	HS code	Average quantity imported per year (kg)	Average quantity exported per year (kg)
Titanium oxides	2823.00	7 373 585	6 842 492
Containing 80% or more by wt of tita dioxide, calculated on the dry matter	3206.11	82 402 444	110 676 653
Pigments and preparations, based on titanium dioxide, nes	3206.19	6 961 041	12 800 515

Abbreviations: HS code, Harmonized System code; HS 6; six digit Harmonized System code; kg, kilograms

3.2.3 Uses

Titanium dioxide, titanium tetrachloride and titanium trichloride are the most abundant titanium compounds in commerce, with titanium dioxide representing 95% of all titanium consumed (Jin and Berlin 2015; Ramoju et al. 2020). The principle use of titanium

mineral is for the manufacture of titanium dioxide pigment which accounts for more than 90% of world titanium mineral consumption (Murphy and Frick 2006 as cited in Woodruff et al. 2017). Titanium metal and alloys have a number of uses in transportation, the chemical industry, and in pulp and paper and medical applications owing to their properties, including high tensile strength, lightweight, chemical inertness, and high corrosion resistance (Jin and Berlin 2015). Titanium dioxide pigment is commonly used in paints and coatings, plastics, cosmetics, and drug products available to consumers due to its low price, high availability, brightness/whiteness and high index of refraction (Jin and Berlin 2015).

According to information submitted in response to a CEPA section 71 survey, substances in the Titanium-containing Substances Group are used in various industrial, commercial and consumer applications (Environment Canada 2013). Activities or uses reported in response to the survey for substances associated with quantities over 1 000 kg in the reporting year include processing intermediates, laboratory substances, fabric and textiles, adhesives and sealants, paints and coatings and water repellants. Activities or uses reported in response to the survey for substances associated with lower quantities (less than 1 000 kg in the reporting year) include apparel and footwear care, automotive care, cleaning and furnishing products, building materials, floor coverings, food packaging materials and electronics. Other uses reported in response to the CEPA section 71 survey beyond those identified here were notified as confidential business information.

Further literature searches indicate that substances in the Titanium-containing Substances Group may also be present in cleaning products, laundry products, dish care products, plastics and rubber products, paper products, catalysts, ceramics, printing ink, stationery products, aerospace applications, marine applications, medical applications, oil and gas products, and specialty chemicals (Woodruff et al. 2017; Health Canada 2019; USGS 2020; CPID [modified 2022]; CPISI [modified 2022]).

Substances in the Titanium-containing Substances Group are present in cosmetics based on notifications submitted under the *Cosmetic Regulations* (personal communication, emails from the Consumer and Hazardous Products Safety Directorate (CHPSD), Health Canada, to the Existing Substances Risk Assessment Bureau (ESRAB), Health Canada, dated between March 29, 2018 and December 8, 2020; unreferenced). The substances in this group are also present as medicinal or non-medicinal ingredients in disinfectants, human and veterinary drug products, as well as in natural health products (personal communication, emails from the Pharmaceutical Drugs Directorate (PDD), Health Canada, to the ESRAB, Health Canada, dated February 16, 2018 and February 26, 2018; unreferenced; personal communication, email from the Natural and Non-prescription Health Products Directorate (NNHPD), Health Canada, to the ESRAB, Health Canada, dated March 9, 2018; unreferenced; DPD [modified 2022]; LNHPD [modified 2022]; NHPID [modified 2022]).

Titanium and its alloys are used in medical procedures, such as dental implants and hip replacements. The health effects related to these uses were not considered in this assessment.

In Canada, substances in the Titanium-containing Substances Group may be used as components in the manufacture of food packaging materials (personal communication, email from the Food Directorate (FD), Health Canada, to the ESRAB, Health Canada, dated March 13, 2018; unreferenced]). Titanium-containing food additives (titanium dioxide, potassium aluminium silicate-based titanium dioxide, and potassium aluminum silicate-based titanium dioxide and iron oxide) are permitted for use as colouring agents in a variety of foods as prescribed in the *List of Permitted Colouring Agents*, incorporated by reference into its respective Marketing Authorization issued under the *Food and Drugs Act* (Health Canada [modified 2021a]). The food additive uses of food-grade titanium dioxide have been evaluated by Health Canada's Food Directorate in the State of the Science of Titanium Dioxide (TiO_2) as a Food Additive, which was published in June 2022 (Health Canada 2022b). In this report, Health Canada's Food Directorate did not identify any conclusive scientific evidence that the food additive titanium dioxide is a concern for human health. Health Canada's Food Directorate will continue to monitor the emerging scientific evidence related to the safety of food uses of titanium dioxide.

Additionally, some substances in the Titanium-containing Substances Group are present in registered pest control products in Canada as formulants (personal communication, email from the Pesticide Management Regulatory Agency, Health Canada, to the ESRAB, Health Canada, dated January 31, 2018; unreferenced).

4. Potential to cause ecological harm

4.1 Characterization of ecological risk

The potential for cumulative effects was considered in this assessment by examining cumulative exposures from the broader moiety of titanium. The ecological risks of the 13 substances in the Titanium-containing Substances Group were characterized using the ERC-I (ECCC 2020). ERC-I is a risk-based approach that employs multiple metrics considering both hazard and exposure, with weighted consideration of multiple lines of evidence for determining risk classification. A summary of the approach is outlined below; the approach is described in detail in the ERC-I science approach document (ECCC 2020).

Hazard characterization in ERC-I included a survey of published PNECs and water quality guidelines from domestic and international assessments. When no suitable existing PNEC or water quality guideline was found, hazard endpoint data were collected and, depending on data availability, either a species sensitivity distribution or an assessment factor (AF) approach was taken to derive a new PNEC value. In the

case of the 13 titanium-containing substances, hazard endpoint data were available from multiple sources including comprehensive literature searches for specific groups, targeted searches of the ECOTOX database and European Chemicals Agency (ECHA) registration dossiers (as described in ECCC (2020)). In the absence of more recent information, the assumptions used in the 2006 categorization of the DSL were also considered (ECCC, HC [modified 2017]). An AF approach was used to derive a PNEC value of 850 µg/L for titanium and a PNEC value of 2 760 µg/L for titanium dioxide (ECCC 2020).

Exposure profiling in ERC-I considered two approaches: predictive modelling using a generic near-field exposure model and an analysis of measured concentrations collected by federal and provincial water quality monitoring programs. The generic near-field exposure model used input data, when available, from the National Pollutant Release Inventory, information submitted in response to CEPA section 71 surveys, international trade data from the Canada Border Services Agency, and third-party market research reports to generate PECs. In the case of the 13 titanium-containing substances, information submitted in response to a CEPA section 71 survey and international trade data from the CBSA were available. Data were available from the NPRI for titanium tetrachloride (as described in ECCC (2020)).

Measured titanium concentrations were available for total and dissolved titanium from the National Long-term Water Quality Monitoring (NLTWQM) network, the Environmental Monitoring System of the British Columbia Ministry of the Environment and Climate Change Strategy, the Surface Water Quality Program of Alberta Environment and Parks, the Regional Aquatics Monitoring Program, the Canada-Alberta Joint Oil Sands Environmental Monitoring program, the Long Term Water Quality Monitoring Network of the Government of Manitoba, Provincial Water Quality Monitoring Network of the Ontario Ministry of the Environment and Climate Change, and the Baseline Monitoring of Lower Order Streams in Saskatchewan. Extractable titanium concentrations were available and compiled from the NLTWQM network for the Atlantic, Pacific, and Northwest Territories region between 2005 and 2015. Exposure profiling using modeled and measured data for the 13 titanium-containing substances resulted in a low exposure classification for each substance.

Measured values and modelled PECs were compared to the PNECs, and statistical metrics that consider both the frequency and magnitude of exceedances were computed and compared to decision criteria to classify the potential for ecological risk. Critical data and considerations used to create substance-specific ecological profiles and classifications associated with ecological risk, as well as identification of potential need for tracking of future use patterns, are presented in ECCC (2020). According to information considered in ERC-I, the overall risk classification for each of the 13 substances in the Titanium-containing Substances Group is low. Based on the outcome of the ERC-I analysis, the 13 titanium-containing substances are considered unlikely to be causing ecological harm.

5. Potential to cause harm to human health

This human health assessment includes characterization of hazard and exposure to microscale (≥0.1 µm) forms of substances in the Titanium-containing Substances Group. Nanomaterials containing titanium (1 to 100 nm) that may be present in environmental media or products are not explicitly considered in the exposure scenarios of this human health assessment but measured concentrations of titanium in the environment or human biomonitoring data could include titanium from these sources. This human health assessment does not explicitly consider the health effects associated with nanomaterials containing titanium. However, health effects from exposure to titanium-containing substances that include both microscale and nanoscale particles (for example, food-grade titanium dioxide) were considered in this human health assessment. The approach for the assessment of the toxicokinetic and the systemic effects of oral exposure to microscale titanium dioxide was primarily based on the State of the Science report published by Health Canada's Food Directorate (Health Canada 2022b).

It should be noted that analytical methodologies used across different studies to determine particle sizes of titanium-containing substances have changed over time.

5.1 Health effects assessment

According to a literature search on the 13 titanium-containing substances in this assessment, toxicokinetic data and toxicity data for oral, dermal and inhalation routes were predominantly available for titanium dioxide, including rutile and anatase forms. Thus, kinetic and toxicity data on titanium dioxide were used as surrogate data for all substances in the Titanium-containing Substances Group.

Several national and international organizations have reviewed the health effects of exposure to titanium-containing substances (that is, titanium dioxide) in the general population (IPCS 1982; NSF 2005; ECETOC 2013; OECD 2013; Ontario 2014; CLH 2016; EFSA 2016, 2021; NICNAS 2016; ECHA 2017; SCCS 2020; FSANZ 2022; Health Canada 2022b). The health effects of workers exposed to titanium dioxide under occupational settings were also assessed by several international organizations, including the American Conference of Governmental Industrial Hygienists (ACGIH) (2009), the International Agency for Research on Cancer (IARC) (2010) and the National Institute for Occupational Safety and Health (NIOSH) (2011).

The key assessments on titanium dioxide for the general population are summarized below.

The United States (US) National Sanitation Foundation (NSF) (2005) derived a reference dose (RfD) for titanium in 2005 based upon a 1979 study by the National Cancer Institute (NCI). The NSF (2005) identified the highest dietary titanium dioxide

concentration administered (that is, 50 000 ppm, 5% w/w TiO_2) as a no-observed-adverse-effects level (NOAEL). This NOAEL was equivalent to 2 680 mg Ti/kg bw/day, which was estimated based on the average food intake and body weights of female F344 rats. NSF (2005) calculated a RfD of 2.7 mg Ti/kg bw/day for titanium using the above NOAEL and an uncertainty factor (UF) of 1000, which in addition to the UFs for interspecies extrapolation (10) and intraspecies variation (10), included an additional UF of 10 to account for database deficiencies, including lack of developmental and reproductive toxicity studies.

In March 2020, the European Commission requested that the European Food Safety Authority (EFSA) conduct a new risk assessment for E171[7] to address any potential uncertainties, including *in vivo* genotoxicity (EFSA 2019a; 2019b). As a result, the EFSA initiated a re-assessment of food-grade titanium dioxide, E171. E171 has been shown to have a high prevalence of nanoscale particles, which may lead to adverse health effects (Bischoff et al. 2021). The final EFSA assessment was published in May 2021. Based on the uncertainties on the available information on particle distribution analysis and health effects analysis, the EFSA Panel on Food Additive and Nutrient Sources Added to Food (ANS) concluded that "E171 can no longer be considered as safe when used as a food additive" (EFSA 2021). EFSA (2021) did not derive a guidance value due to the above-listed uncertainties in the health effects dataset associated with titanium dioxide (E171) food additives. The EFSA (2021) conclusion was predominantly based on evidence from studies conducted using nanoscale titanium dioxide or studies where E171 was present in simpler matrices that used sonication techniques for particle dispersion. However, it should be noted that while sonication is a common procedure used in nanotoxicity testing protocols (Jensen et al. 2011), it is not a technique used in food manufacture and these studies are not relevant to the assessment of dietary exposure to food-grade titanium dioxide.

In 2022, the European Commission requested that the Scientific Committee on Consumer Safety (SCCS) re-assess the safety of titanium dioxide in cosmetic products with a focus on genotoxicity, and exposure via the inhalation and oral routes, based on the evidence considered in the EFSA re-evaluation in 2021 (EC 2022a).

[7] E171 is the European designation for TiO_2 that meets food additive specifications set out in Commission Regulation (EU) No 231/2012 of 9 March 2012 laying down specifications for food additives listed in Annexes II and III to Regulation (EC) No 1333/2008 of the European Parliament and of the Council.

In June 2022, Health Canada's Food Directorate published a State of the Science concerning the safety of titanium dioxide as a food additive (Health Canada 2022b). The State of the Science presents the safety assessment of the food additive use of titanium dioxide based on an in-depth review of available toxicokinetic and hazard data on titanium dioxide, including several significant new pieces of information that were not available to the ANS panel at the time of their assessment. The review focused on studies conducted with food-grade titanium dioxide (also referred to as E171 according to European labelling requirements for food additives), which is a mixture of nanoscale and microscale titanium dioxide particles (Health Canada 2022b). After reviewing the available data, the Health Canada Food Directorate's State of the Science determined "there is no conclusive scientific evidence that the food additive titanium dioxide is a concern for human health". Similar to Health Canada's Food Directorate (2022), Food Standards Australia New Zealand (FSANZ 2022) and the UK Committee on Toxicity of Chemicals in Food, Consumer Products and the environment (COT 2022) were not in agreement with the EFSA (2021) conclusion on food-grade titanium dioxide.

Information for the health effects section of this assessment was predominantly obtained from existing assessments, and primary literature was reviewed where needed.

5.1.1 Toxicokinetic data and biomarker adequacy

The toxicokinetic data described in this section were primarily limited to those conducted on microscale (≥100 nm) titanium-containing substances. In general, titanium absorption from the gastrointestinal tract (GIT) is low in humans and experimental animals (Perry and Perry 1959; Schroeder et al. 1963; MacNicoll et al. 2015; Farrell and Magnuson 2017; Winkler et al. 2018; Health Canada 2022b). Jones et al. (2015) estimated less than 0.1% of maximum oral absorption when human volunteers were given a single dose of 5 mg TiO_2/kg bw (< 5000 nm) dispersed in water. Based on the data obtained from repeated oral administration of titanium dioxide (particle size of 500 nm) to rats for 10 days, Jani et al. (1994) proposed a blood uptake of 0.02%. The study also estimated an oral absorption of 6.5% after accounting for the total tissue distribution of titanium (Jani et al. 1994). Similarly, after repeated oral administration of titanium dioxide [particle size of 140 to 150 nm for two test articles (that is, NM-101 and NM-102)], Geraets et al. (2014) estimated approximately 0.02% oral absorption in rats based on the total recovery of titanium (mean particle size in the range of 38 to 186 nm) in all tested organs (that is, liver, spleen and mesenteric lymph nodes). This estimate by Geraets et al. (2014) is in line with the absorption fraction of micro titanium dioxide reported by Jani et al. (1994). Other authors indicated a lack of oral absorption based on insignificant translocation of titanium microparticles from the GIT to other tissues after a single administration of microscale titanium dioxide (particle size 120 and 5 000 nm) to rats (MacNicoll et al. 2015) or repeated administration to rats or mice (particle size ranging up to 250 nm) (Farrell and Magnuson 2017; Yan et al. 2020). After evaluating the body of evidence available for titanium absorption, the EFSA (2016) panel determined that the oral bioavailability of titanium (measured as titanium dioxide)

is in the range of 0.02% to 0.1%. Based on the assumptions that most titanium in the body is present in the liver and spleen and that all titanium in the body is derived from dietary sources (that is, the use of titanium dioxide as a food additive), the EFSA (2021) panel estimated the oral systemic availability of titanium dioxide in humans to be less than 1%, at most. Of note, the primary focus of most of these toxicokinetic studies was on the kinetic properties of nanoscale titanium dioxide (for example, Geraets et al. 2014; Jones et al. 2015).

Titanium absorption from the GI tract occurs as a bi-modal pattern in humans, with peaks reported around 2 and 6 hours following intake of titanium dioxide (particle size ranged from 160 to 380 nm) (Böckmann et al. 2000; Pele et al. 2015). Early absorption is most likely from the proximal region of the small intestine (that is, duodenum and jejunum), while late absorption is expected from the distal region (Pele et al. 2015). According to the microscopic imaging, an uptake of titanium (from food-grade titanium dioxide, E171) through Peyer's patches (gut-associated lymphoid tissues) located in the distal region (ileum) of the small intestine was reported by several authors (Shepherd et al 1987; Pele et al. 2015; Bettini et al. 2017; Coméra et al. 2020; Riedle et al. 2020). Bettini et al. (2017) suggested that titanium dioxide may also be absorbed from the colon when rats were exposed to E171.

In experimental animals, the rate of oral absorption is likely determined by the particle size. Small particles sizes were noted to have faster absorption rates, relative to larger particles in experimental animal studies, but the effects of particle size on absorption rate are not clearly demonstrated in humans (MAK 2014; Jones et al. 2015). Available data suggest that physiological conditions (for example, stomach pH) do not affect the solubility of titanium (Winkler et al. 2018).

According to the available *in vivo* (humans or experimental animals) or *in vitro* (human skin penetration tests) data, dermal penetration of microscale titanium dioxide was not detected (Pflücker et al. 2001; Mavon et al. 2005; Sadrieh et al. 2010). When human volunteers repeatedly applied titanium-containing sunscreen (microscale particles) and examined the biopsy materials using X-ray fluorescence analysis, titanium was only seen at the outermost layer of the epidermis (Lademann et al. 1999). Sadrieh et al. (2010) also reported similar findings when sunscreen containing titanium dioxide (300 to 500 nm) was repeatedly applied to minipigs.

There was no convincing evidence for systemic absorption of titanium particles via the respiratory tract (MAK 2014). However, prolonged retention of inhaled particles was observed in experimental animals (Bermudez et al. 2002). Retention time depends on the exposed concentration and the species tested (Bermudez et al. 2002).

Following ingestion of titanium dioxide (particle size 155 nm), the highest concentrations were reported in the spleen, followed by lungs and brain (Wang et al. 2007; EFSA 2016, 2021). After single or repeated intravenous injections of pigment-grade titanium dioxide (mean particle size of 267 nm), accumulation was highest in the liver followed by

spleen, lungs and kidneys (Geraets et al. 2014). Some human and animal studies conducted on microscale titanium exposed via the oral route have reported relatively high titanium concentrations in lungs, probably from the retention of inhaled titanium from contaminated dust present in the environment (Schroeder et al. 1963; Wang et al. 2007). After analyzing human placentas (n=22) and meconium samples (n=18), Guillard et al. (2020) showed that a small concentration of ingested titanium can be systemically available to the developing fetus. Using an *ex vivo* human placenta perfusion model, the authors further demonstrated that a small amount of titanium dioxide (E171) [55% nanoscale particles, measured by scanning electron microscopy (SEM)] could cross placental membranes to the fetal side. Additional analysis revealed that 75% to 100% of particles transferred to the fetal side were in the nano-sized range.

Greater than 96% of orally administered titanium (predominantly as titanium dioxide) is unabsorbed and excreted in the feces (Schroeder et al. 1963; Jovanović 2014; Jin and Berlin 2015). Of the orally absorbed fraction of titanium (microscale), less than 2% and 3% is excreted in the urine in experimental animals and humans, respectively, with the rest being eliminated in feces (Perry and Perry 1959; Schroeder et al. 1963; EFSA 2016, 2021; Farrell and Magnuson 2017). Clearance of titanium from the body is prolonged; the biological half-life for titanium was estimated to be an average of 320 days or longer in humans, 640 days in mice and 450 days in rats (IPCS 1982; Geraets et al. 2014; Jin and Berlin 2015). Some authors have indicated titanium dioxide could interact with gut microbiota before elimination (Pinget et al. 2019; Talamini et al. 2019; Lamas et al. 2020). The EFSA (2021) panel considered the current knowledge to be insufficient to make any conclusion regarding the effects of E171 on gut microbiota and related health effects.

The retention half-life of inhaled titanium dioxide varies with particle size and concentration (Kawasaki 2017). In rats, the lung retention half-lives of microscale particles [(rutile; mass median aerodynamic diameter (MMAD) of particle size was 144 nm)] were 100, 324 and 838 days for exposure concentrations of 10, 50 and 250 mg/m^3, respectively (Bermudez et al. 2002). Warheit et al. (1997) have reported somewhat shorter retention times than Bermudez et al. (2002). According to Warheit et al. (1997), deposited titanium dioxide (four-week exposure, pigment-grade rutile type, size of primary particles: 200 to 300 nm) in rat lungs was cleared with elimination half-lives of 68, 110 and 330 days for the 5, 50 and 250 mg/m^3 groups, respectively. EFSA (2016) further proposed that the slow elimination of titanium is likely to indicate a potential for slow, but steady titanium accumulation in the body.

The concentration of titanium in blood represents the bioavailable fraction, which is the fraction systemically available at target sites. Continuous exposure is expected in the general population because the primary sources of titanium exposure are food and environmental media. With frequent exposure from diet titanium is likely at a steady state in the blood. Dosing studies in humans and animals show measurable increases in blood titanium concentrations after oral ingestion of known quantities of food-grade titanium dioxide (primarily microscale particles) (Ramoju et al. 2020). Böckmann et al.

(2000) reported peak blood concentrations of 43.2 (n=5) and 61.8 µg/L (n=2) after administering capsules containing microscale titanium dioxide at 22.9 or 45.8 mg, respectively. Using a comparable trial design with human volunteers, Pele et al. (2015) reported a similar pattern of titanium absorption into the blood after oral administration. A small but dose-related increase in titanium concentration in blood was also reported in some treated groups in an extended one-generation reproductive (EOGRT) study in rats (REACH [modified 2022]). Thus, the titanium concentration in whole blood is considered a suitable biomarker to quantify systemic exposure from all routes to all sources of titanium for the purposes of this human health assessment.

5.1.2 Health effects of oral exposure

Titanium is not considered an essential element and there are no beneficial effects of titanium consumption for humans (IPCS 1982). In the current assessment, it is assumed that titanium is the toxicologically relevant moiety for the systemic health effects of titanium-containing substances. Where applicable, administered or systemically exposed doses from titanium-containing substances were converted to equivalent elemental titanium doses using molecular weight conversion.

Acute toxicity:

Two studies, conducted according to the Organisation for Economic Co-operation and Development (OECD) test guidelines (TG) 420 (in male and female mice) and 425 (in female rats), reported an acute oral median lethal dose (LD_{50}) of greater than 5 000 mg TiO_2/kg bw (3 114 mg Ti/kg bw) (OECD 2013). EFSA (2016) has reported LD_{50} values for titanium dioxide in mice and rats as >10 g TiO_2/kg bw/day and >25 000 mg TiO_2/kg bw/day, respectively.

Wang et al. (2007) did not report significant changes in body weight or organ weights (that is, liver, spleen and kidneys) or serum biochemical parameters in male and female Charles River (CD-I) mice at 2 weeks post-exposure to a single oral gavage dose of micro titanium dioxide (particle size 155 nm) at 5 000 mg TiO_2/kg bw/day (3 114 mg Ti/kg bw/day) compared to control animals. There were no adverse pathological changes in the heart, lung, testicle or ovary, and the spleen tissues of the treated male and female mice. However, histopathological evaluation of treated male and female animals indicated fatty degeneration induced in the hippocampus, swelling in renal glomerulus, spotty necrosis of hepatocytes (female only) and hydropic degeneration around the central vein of the liver. While authors reported these effects were found for both nanoscale and microscale particles (80 and 155 nm, respectively), the EFSA (2016) panel indicated that the above effects were only associated with nanoscale particles (80 nm).

Based on the available key reviews (OECD 2013; EFSA 2016, 2021), microscale titanium displays low acute toxicity via the oral route.

Short-term and sub-chronic toxicity:

In a 28-day study (OECD TG 407), male Sprague-Dawley (SD) rats were administered one of two types of rutile pigment-grade titanium dioxide (median particle size-D_{50} of 173 nm) at a dose of 24 000 mg/kg bw/day (equivalent to 14 946 mg Ti/kg bw/day) via oral gavage. No significant changes in body and organ weights, or gross pathology were observed, and the authors concluded that the dose tested was the NOAEL (OECD 2013; Warheit et al. 2015a).

The same authors conducted a 90-day toxicity study following OECD TG 408. Male and female SD rats were administered surface-coated pigment-grade titanium dioxide (D_{50} of 145 nm by number) at 0, 100, 300, or 1 000 mg/kg bw/day (0, 62, 187 or 623 mg Ti/kg bw/day, respectively) by oral gavage. Animals were evaluated for food consumption, body weight, neurobehavioral effects, clinical pathology, hematology, clinical serum chemistry and urine analysis. None of the exposed animals showed any significant treatment-related effects and, therefore, the authors determined that the NOAEL for 90-day exposure was 623 mg Ti/kg bw/day (Warheit et al. 2015a).

Another 90-day range-finding study for chronic carcinogenicity, conducted by the NCI (1979), analyzed the toxicity of anatase titanium dioxide in Fischer 344 rats. Rats (10/sex/dose) were administered titanium dioxide at doses of 6 250, 12 500, 25 000, 50 000 or 100 000 mg/kg in the diet [equivalent to 569, 1 138, 2 275, 4 550 or 9 100 mg TiO_2/kg bw/day for female rats and 506, 1 013, 2 025, 4 050 or 8 100 mg TiO_2/kg bw/day for male rats, respectively; dose conversion as per EFSA (2016)]. The original study did not report particle size; however, the Health Canada Food Directorate's (2022b) State of the Science indicated a particle size in the range of 113 to 135 nm and 109 to 124 nm by SEM and transmission electron microscopy (TEM), respectively, with up to 44% of particles (by number) as nanoscale particles.

The NCI (1979) also administered the same dose levels in diet for 90 days in male and female B6C3F1 mice [highest dose tested was equivalent to 21 500 mg TiO_2/kg bw/day (10 000 mg Ti/kg bw/day) in female mice and 16 000 mg TiO_2/kg bw/day (13 400 mg Ti/kg bw/day) for male mice according to EFSA (2016) estimates]. No treatment-related adverse effects were observed in either species at any of the doses tested. The NCI (1979) study did not analyze hematological parameters or biochemical parameters in the urine and blood of rats or mice.

In a recent study, Heo et al. (2020) also established a NOAEL of 1 000 mg TiO_2/kg bw/day (623 mg Ti/kg bw/day), which was the highest dose tested for agglomerated/aggregated titanium dioxide (P25; particle diameter of agglomerated/aggregated titanium dioxide, P25 was approximately 180 nm) in 28- and 90-day oral toxicity studies in SD rats. Another study by Han et al. (2020) also did not report effects on clinical appearance, survival, body weight, feed intake, haematology, clinical chemistry, urinalysis, organ weights, or gross and microscopic pathology in rats administered food-grade titanium dioxide (E171) via gavage at 1000 mg TiO_2/kg bw/day

for 90 days. While the authors reported a 6% to 10% higher feed intake in male rats at 1000 mg TiO_2/kg bw/day, there were no associated changes in body weight. Authors also reported an 8% decrease in relative lymphocyte counts in low- and high-dose males. Due to mild effects and inconsistent dose-response, EFSA (2021) panel considered 1 000 mg TiO_2/kg bw/day as the overall NOAEL from this study.

The potential for inflammation and immunotoxic effects from exposure to titanium dioxide has been investigated in a series of short-term and sub-chronic studies in experimental animals. Riedle et al. (2020) reported no significant differences in inflammation or effects on immune cell populations in Peyer's patches of male and female mice (n=6/sex/dose) administered E171 in diet (particle diameter range from 50 to 350 nm) at 0, 1, 10,-or 100 mg TiO_2/kg bw/day for 18 weeks.

In another study, Blevins et al. (2019) examined immunological effects in rats associated with dietary intake of E171. In this study, male rats were exposed to E171 (anatase, 110 to 115 nm, 36% nanoscale particles, analyzed by SEM) in a standard diet at a dose of 0, 40, 400 or 5,000 mg/kg diet for 7 days (n = 5 animals/dose; dose equivalent to 1.8, 4.8, 31.4, 374 mg/kg bw per day, respectively) and 100 days (n = 15 animals/dose; equivalent to 1.3, 3.5, 22.4 or 267 mg/kg bw per day, respectively). Dose conversions were based on EFSA (2021) assessment. At the start of the study a separate set of rats (n = 5 to 8 animals) were treated with a single intraperitoneal injection of a sterile dose of 180 mg/kg bw dimethylhydrazine (DMH) dihydrochloride as a positive control. Authors did not observe acute or sub-chronic inflammation or effects on the immune system when male rats were exposed to E171.

An EOGRT study reported in REACH ([modified 2022]) (described under reproductive and developmental effects) examined developmental immunotoxicity and did not report immunotoxicity effects in rats.

Conversely, Bettini et al. (2017) reported immune-suppressive effects in the gut of male rats (n=10) exposed to E171 (anatase; D_{50} 118±53 nm, range 20 to 340 nm, containing 44.7% nanoscale particles, analyzed by TEM) and ultra-sonicated titanium dioxide nano particles (NM-105, particle size 10 to 45 nm) in water [using NANOGENOTOX protocol (Jensen et al. 2011)]. The animals were exposed via intragastric gavage to E171, dispersed in water, at 10 mg TiO_2/kg bw/day for 7 days. Rats in this series of the experiments were used for tissue imaging, flow cytometry and cytokine assays to investigate tissue inflammation and gut permeability measurements. To study *ex vivo* immune cell responses, the authors isolated total immune cells from Peyer's patches and the spleen of untreated rats. These isolated cells were treated *ex vivo* with E171 and NM-105 and then were cultured with anti-CD3/CD28 antibodies to induce cytokine secretion into the culture media. All E171-treated isolated immune cells from Peyer's patches showed a decrease in T-helper (Th)-1 IFN-γ secretion, while splenic Th1/Th17 inflammatory responses sharply increased. Since these effects were more pronounced in cells treated with E171 compared to NM-105, the authors determined that microscale particles likely caused immuno-suppression. Bettini et al. (2017) also exposed rats for

100 days to 10 mg TiO_2/kg bw/day via drinking water. Only E171-treated animals for 100 days showed micro inflammatory effects in the colon. No significant change in paracellular epithelial permeability was observed in the E171-treated rats for 7 or 100 days in comparison to the controls. Based on the study results, the EFSA (2021) panel considered E171 has proinflammatory potential at the systemic level.

Similarly, Han et al. (2020) reported a slight, but statistically significant decrease in relative lymphocyte count (~8%) in high- and low-dose males, approximately 40% decrease in granulocyte-macrophage colony-stimulating factor in females and alterations in plasma Immunoglobulin M (IgM) in both sexes at the highest dose tested, when male and female rats were administered E171 at 10, 100 or 1 000 mg TiO_2/kg bw/day via gavage for 90 days. However, the EFSA (2021) panel considered the highest dose tested was a NOAEL due to lack of dose-response and natural variability in these parameters.

Studies by Urrutia-Ortega et al. (2016) (dosing at 5 mg TiO_2/kg bw/day via gavage for 10 weeks) and Talamini et al. (2019) (dosing of mice at 2 mg TiO_2/kg bw/day via drinking water for 3 weeks) reported modest inflammation or immunotoxicity effects in the gut when experimental animals were exposed to E171 at low dose levels. The results of these studies were considered less reliable, as the studies were not conducted according to a test guideline and limited to one dose level. The EFSA (2021) panel also considered that the modest immunological effects reported in Talamini et al. (2019) can not be identified as adverse because similar effects were observed in control animals. In addition, the biochemical changes in the stomach and small intestine were considered as adaptive responses to oxidative stress, not an evidence of adversity. A detailed analysis of immunological effects can also be found in the State of the Science published by Health Canada's Food Directorate (2022b).

Based on available key reviews and studies (NCI 1979; OECD 2013; Han et al. 2020; REACH [modified 2022]), microscale titanium displays low toxicity following short-term and sub-chronic exposure when administered via the oral route. Of note, the studies that reported adverse effects were administered either by gavage or through drinking water, and none of the dietary studies reported adverse effects in experimental animals.

Reproductive and developmental toxicity:

Warheit et al. (2015b) administered titanium dioxide (D_{50} 153 to 213 nm) in sterile water at a dose of 0, 100, 300, or 1 000 mg/kg bw/day (0, 62, 187 or 623 mg Ti/kg bw/day, respectively) by oral gavage during gestation day 6 to 20 and 5 to 19 to SD and Wistar rats (22 animals/dose), respectively. The study design was compiled of several test guidelines, including OECD TG 414 (prenatal developmental toxicity study). Maternal animals were monitored for body weight changes, food consumption, and clinical observations during the experiment. At the end of gestation, dams were euthanized, and the uterine contents were examined, including counts of corpora lutea, implantation sites, resorptions, and live and dead fetuses. Fetuses were examined for sex, body

weight and skeletal malformations. Additionally, fresh visceral and head examinations were performed on selected fetuses. There was no evidence for any treatment-related maternal or developmental effects in any animals for any of the doses tested. The authors concluded that the NOAEL for developmental toxicity for titanium dioxide was 1 000 mg TiO_2/kg bw/day (623 mg Ti/kg bw/day), which was the highest dose tested.

An EOGRT study with E171 was conducted according to OECD TG 443 and was compliant with good laboratory practice (GLP). In the study, SD rats were exposed to E171 (anatase, D_{50} = 100 nm, 50% of the individual particles <100 nm) at a dose of 0, 100, 300 or 1 000 mg TiO_2/kg bw/day (0, 62, 187 or 623 mg Ti/kg bw/day, respectively) in diet (REACH [modified 2022]). The basal diet contained roughly 17 mg Ti/kg feed (range of 11 to 31 mg Ti/kg feed), which was estimated to be equivalent to approximately 1.4 mg TiO2/kg bw/day (EFSA 2021). Palatability of feed was not altered in animals dosed up to 1 000 mg TiO_2/kg bw/day in a previous study (REACH [modified 2022]). Sexually mature male and female rats (F0 generation, 24 rats/dose/sex) were exposed to titanium dioxide in diet starting two weeks before mating and continuously through mating, gestation and weaning of the pups (F1 generation). The F1 generation received the same dose levels in diet from weaning until post-natal day (PND) 4 of the F2 generation. At weaning, F1 pups were assigned to satellite groups for reproductive/developmental toxicity testing, developmental neurotoxicity testing and immunotoxicity testing. F2 pups were exposed to treatment in utero and via milk until termination on PND 4.

Treated F0 generation animals did not exhibit any test article-related effects in estrous cycle in female animals or sperm parameters (that is, sperm count, sperm viability and sperm morphology) or organ weights (that is, epididymides and testicles) of the male animals (REACH [modified 2022]). There were no adverse effects in reproductive performance and no treatment-related effects observed in pups for development and developmental neurotoxicity in satellite groups of the F1 generation up to 1 000 mg TiO_2/kg bw/day. The study authors concluded that the NOAEL for reproductive and developmental toxicity of titanium dioxide was 1 000 mg TiO_2/kg bw/day (623 mg Ti/kg bw/day) (REACH [modified 2022]). The EFSA panel (2021) agreed with the authors' conclusion for reproductive and developmental toxicity.

The EOGRT study also examined developmental immunotoxicity. A satellite group of F1 generation male and female rats (10/sex/dose) were pretreated with keyhole limpet haemocyanin (KLH) antigen and exposed to E171 in the diet at 0, 100, 300 or 1 000 mg TiO2/kg bw/day for 10 weeks. Cyclophosphamide (CY), which is a known immunosuppressant was used as a positive control for the KLH assay. Animals were treated with E171 and CY at different time points and therefore, the study did not include a concurrent control for the CY response. Thus, the EFSA (2021) panel determined that the positive control was not valid and therefore, test sensitivity is not clearly demonstrated in this portion of the study. The spleens of the animals were removed and cut in two. One half was used for histopathology and the other half was used to obtain a cell suspension for the analysis of lymphocyte subpopulations. A single

cell suspension was prepared and lymphocyte subpopulations of T cells, T helper cells, T suppressor/cytotoxic cells, NK cells and B cells were determined by flow cytometry analysis (FACS). It should be noted that flow cytometry analysis of splenic cell suspensions was conducted at separate time points, which could have an influence on the staining and quantification.

Treated male rats showed a marginal, but statistically significant decrease (9%) in the antigen-induced IgM level at the highest dose tested (1 000 mg TiO2/kg bw/day). Both male and female animals did not show treatment-related effects in hematology, spleen weight, histopathology of lymphoid organs (that is, spleen, thymus, lymph nodes, and bone marrow), total and differential peripheral white blood cells count, and splenic lymphocyte subpopulation in both sexes. While all treated animals showed weak immunogenic response to the antigen, these effects were insufficient to identify T cell-dependent immunotoxic effects of E171 (REACH [modified 2022]). The authors indicated that the immune response was not adversely affected by E171 as explained by KLH assay. The EFSA (2021) panel disagreed, indicating that it was unable to decide on the association of E171 on developmental immunotoxicity.

As opposed to the observations of the EOGRT study, Schroeder and Mitchener (1971) reported a significant reduction in the survival of Long Evans (blue spruce) rat offspring in the second generation of a three-generation reproduction toxicity study. However, the applicability of this study was limited as the type of titanium compound used was not reported and only a single dose level was tested.

Based on the available key reviews and studies (EFSA 2021; REACH [modified 2022]), microscale titanium displays low reproductive and developmental toxicity.

Genotoxicity:

After reviewing a large body of evidence, international assessments, such as IARC (2010), NICNAS (2016), ECHA (2017), EFSA (2016, 2018, 2019 a,b), and SCCS (2020) did not raise any concern over the genotoxic potential of titanium dioxide.

Since the publication of previous assessments, EFSA (2021) re-evaluated the potential genotoxicity of food grade titanium dioxide, E171. The genotoxicity studies considered in the re-evaluation include studies conducted on E171 (a mixture of microscale and nanoscale titanium dioxide particles), non-food-grade titanium dioxide particles, and non-food-grade nanoscale titanium dioxide particles. For the current human health assessment of microscale titanium dioxide, genotoxicity studies conducted on microscale titanium dioxide or a mixture of microscale and nanoscale particles, including food-grade and non-food grade titanium dioxide were considered relevant. A detailed analysis of the genotoxicity of titanium dioxide can also be found in EFSA (2021) and Health Canada Food Directorate’s State of the Science of Titanium Dioxide as a Food Additive (2022b). Relevant studies for the current human health assessment

are primarily based on EFSA (2021) and Health Canada (2022b) and they are summarized below.

In vitro genotoxicity of titanium dioxide:

There were no *in vitro* genotoxicity studies conducted on titanium dioxide microscale particles, but DNA damage as assessed by comet assay and micronucleus (MN) test is available for titanium dioxide nanoscale and microscale particle mixtures.

Proquin et al. (2017), Dorier et al. (2017), Dorier et al. (2019) and Franz et al. (2020) studied DNA damage associated with E171 using the comet assay. Proquin et al. (2017) assessed the acute DNA damage of E171 by comet assay using human colon carcinoma cell line (Caco-2). Cells were exposed to single, non-cytotoxic concentration of E171 at 0.143 µg/cm^2 [with or without co-exposure of azoxymethane (AOM)] for 24 hours. DNA damage is represented by the median tail intensity of the comet. The experiment includes a control and hydrogen peroxide (H_2O_2) positive control. Results showed E171 induced single-strand DNA breaks with or without AOM co-exposure. Cell toxicity was not observed during the assay. However, the results of this study have limited reliability because only a single concentration was tested. Dorier et al. (2017) also reported positive results following repeated exposure (3 weeks) of Caco-2 cell line to 10 or 50 µg/mL E171. The study is also limited because results were insufficiently reported. Another study by Franz et al. (2020) reported negative results in the comet assay when colon cancer cell line (HT29-MTX-E12) were exposed to 0, 0.5, 5 or 50 µg/mL of E171 for 48 hours. In a study considered to be highly reliable by the EFSA (2021) panel, negative results were reported when Brown et al. (2019) exposed to Caco-2 cell line to E171 at concentrations of 3.13, 6.25, 12.5, 25, and 50 µg/ml for 4 hours. Similarly, Dorier et al. (2017) and (2019) reported negative results following acute exposure (6 or 48 hours and 24 hours, respectively) of a Caco-2 cell line to 10 or 50 µg/mL and 50 µg/mL E171, respectively. Studies by Dorier et al. were noted to have various limitations, including insufficiently reported results or testing only a single test concentration (2019 study).

EFSA (2021) also reported mixed results in the comet assay in several studies that used non-food grade forms of titanium dioxide containing a mixture of nanoscale and microscale particles and results of those studies are summarized below.

DNA strand break was also studied using comet assays performed with non-food grade titanium dioxide containing a mixture of nanoscale and microscale particles (Bhattacharya et al. 2009; El Yamani et al. 2017; Andreoli et al. 2018; Vila et al. 2018; Brzicova et al. 2019; Murugadoss et al. 2020; Zijno et al. 2020). Andreoli et al. (2018) reported positive results in a comet assay performed using human peripheral blood mononuclear cells (PBMCs) treated with titanium dioxide with different particle sizes (particle size measured by TEM: anatase/rutile, 45 to 262 nm; anatase, 50 to 270 nm or rutile, 50 to 3000 nm) at concentrations of 10, 50, 100, or 200 µg/mL for 24 hours. Study authors reported statistically significant increases in single strand breaks in PBMCs for

all forms of titanium dioxide. Single strand breaks were only statistically significant at the highest dose tested for both anatase and rutile titanium dioxide, while statistically significant results were reported from 50 µg/mL and above for the anatase/rutile mixture (Andreoli et al. 2018).

Similarly, El Yamani et al. (2017), Murugadoss et al. (2020) and Zijno et al. (2020) all reported positive results for comet assays performed with titanium dioxide with particle sizes in the range of 50 to 150 nm. Equivocal results were reported by Vila et al. (2018) and Brzicova et al. (2019) for the same range of particle size, whereas Bhattacharya et al. (2009) reported negative results for titanium dioxide particles (50 to 150 nm) in the comet assay. The EFSA (2021) panel considered all the above-mentioned studies with non-food grade titanium dioxide (with a mixture of nano and micro particles) as highly reliable studies. El Yamani et al. (2017) also performed a comet assay using human lymphoblastoid cell (TK6) [in addition to human alveolar carcinoma cells (A549)], the reliability of this portion of the study is low due to slightly low cell viability.

Proquin et al. (2017) and Franz et al. (2020) have conducted *in vitro* chromosomal aberrations/ mammalian cell MN tests using E171. Proquin et al. (2017) reported positive results in the MN test when a human colon adenocarcinoma cell line (HCT116) was treated for 24 hours with E171 at concentrations of 50,100, 500 or 1000 µg/mL. EFSA (2021) assigned limited reliability to this study due to lack of a positive control and independent replicates. In contrast, Franz et al. (2020) reported negative results in a MN test in the HT29-MTX-E12 cell line when exposed to 0.5, 5 and 50 µg/mL of E171 (170 nm). The E171 suspensions used in this study were intentionally prepared to generate large agglomerates that represent the particle size distribution of E171 in the food matrix. The reliability of the negative results in the Franz et al. (2020) study is difficult to interpret as the agglomeration status of the particles in the exposure media was not confirmed and the agglomerates themselves interfered with the detection of micronuclei in the flow cytometry-based scoring method used by the authors (Health Canada 2022b). Additionally, the authors did not evaluate the cellular uptake of the particles (Health Canada 2022b). EFSA (2021) also considered this study to have low reliability due to methodological limitations, including an insufficiently reliable flow cytometry approach. The detection of micronuclei in the flow cytometry was interfered by the presence of intentionally created large titanium dioxide agglomerates for the study.

Several other studies conducted using non-food grade titanium dioxide containing both nanoscale and microscale particles reported mixed results (Uboldi et al. 2016; Di Bucchianico et al. 2017; Andreoli et al. 2018; Zijno et al. 2020). Positive MN results were reported by Uboldi et al. (2016) when a Balb/c 3T3 (Mouse embryo fibroblasts) cell line was exposed to titanium dioxide (60 to 400 nm) at a concentration of 10 µg/mL for 72 hours. EFSA (2021) considered this study to have limited reliability because the study only included a single concentration. However, several other studies, which were rated as highly reliable studies by EFSA (2021) reported negative results in MN tests for titanium dioxide with mixed nanoscale and microscale particles [Di Bucchianico et al.

2017 (50 to 150 nm); Andreoli et al. 2018 (45 to 262 nm); Zijno et al. 2020 (50 to 150 nm)].

In vivo genotoxicity of titanium dioxide:

In vivo genotoxicity as assessed by comet assay and MN test are available for both E171 and non-food grade titanium dioxide microscale particles (>100 nm) (EFSA 2016; EFSA 2021).

Sycheva et al. (2011) and Murugadoss et al. (2020) reported positive results on comet assays following gavage administration of titanium dioxide. Sycheva et al. (2011) exposed male mice (n = 5 per group) to titanium dioxide (anatase; 160 ±59 nm – measured by electron microscopy) at 40, and 200 mg TiO_2/kg bw, daily for 7 days and examined the potential to induce DNA damage in the liver, brain, and bone marrow cells 24 hours after the last treatment. No positive control group was included. A statistically significant increase in mean % tail DNA was observed at both doses for the bone marrow test. No DNA damage was observed for liver or brain cells. EFSA (2016) considered the study to be of limited reliability due to study limitations, including lack of positive control and lack of information on organ toxicity. Heath Canada (2022b) has discussed several additional limitations, including lack of dose-response and deviation from the OECD test guideline 489 (for example, only used two dose levels, analysis of DNA damage 24 hours after treatment instead of standard 2 to 6 hours after the treatment), amongst other limitations.

Murugadoss et al. (2020) exposed female mice (n= 4 to 5 per group) to titanium dioxide (anatase; 117 nm – measured using TEM) at 10, 50, 250 µg TiO_2/mouse via oral gavage and evaluated DNA damage in peripheral blood cells. The titanium dioxide suspensions used in the study were composed of either small or large agglomerates with similar dispersion medium composition. Untreated animal blood exposed to H_2O_2 100 µM for 15 min served as positive control. Blood samples were collected 3 days after treatment and analyzed in an alkaline comet assay. Significantly positive results for the comet assay were reported for all three dose groups; yet there was no significant quantitative difference in the DNA damage between mid and high doses. EFSA (2021) considered this study to be of low reliability due to the lack of dose-response. Due to limitations of the study protocol (see State of the Science, Health Canada 2022b for details), Health Canada Health Canada's Food Directorate considered the results of this study as equivocal (Health Canada 2022b).

In contrast, Bettini et al. (2017) and Jensen et al. (2019) reported negative results for *in vivo* comet assays with E171. Jensen et al. (2019) administered 50 or 500 mg TiO_2/kg bw of E171 [anatase; three size groups of particles: 135, 305, 900 nm (TEM image)] to rats (10/group) once a week, over 10 weeks. At 24 hours after the last dose, liver and lung cells were analyzed for DNA damage by an alkaline comet assay [with or without formamidopyrimidine-DNA glycosylase (Fpg)]. Authors reported negative results for DNA damage in lung and liver tissues with all three particles sizes. While EFSA (2021)

considered this study as highly reliable and relevant, Health Canada's Food Directorate (2022b) considered it to be difficult to interpret the negative results due to several study limitations, including a deviation of the test protocol from the OECD TG 489, including the use of only two dose groups, the analysis of DNA damage 24 hours after last exposure instead of 2 to 6 hours after the last dose, and an outdated dosing regime and visual scoring method for DNA damage instead of automated or semi-automated image analysis software. In addition, due to the low bioavailability of titanium dioxide via the GIT, it is unclear whether the systemic exposure is large enough to initiate DNA damage in lung and liver tissues. Negative results for DNA damage were also reported by Bettini et al. (2017), when adult male Wistar rats were exposed to 10 mg TiO_2/kg bw/day of E171 (anatase; D_{50} 118±53 nm, range 20 to 340 nm, with 44.7% of particles < 100 nm as determined by TEM) through oral gavage for 7 days. No positive control was included in the study. At the end of dosing (time is not specified), cells from the Peyer's patch were collected for DNA strand breaks using an alkaline comet assay with or without Fpg. Authors reported negative results for the DNA strand breaks and oxidative DNA damage. The Bettini et al. (2017) study also had several limitations, including the deviation of test protocol from OECD TG 489 (for example, only a single dose tested and the lack of positive control).

Few authors assessed the potential for titanium microscale particles to induce MN using *in vivo* studies that administered titanium dioxide either via oral or intraperitoneal (i.p.) injection (Shelby et al*.* 1993; Shelby and Witt 1995; Sycheva et al*.* 2011; Donner et al*.* 2016). According to EFSA (2021) analysis, Shelby et al. (1993) and Shelby and Witt (1995) reported equivocal results for the MN test when male mice (n = 5) were administered titanium dioxide (Unitane® 0-220, > 100 nm) via i.p. injection for 3 days. Two experiments with different dose levels were tested: 1) 250, 500 or 1000 mg TiO_2/kg bw and 2) 500, 1000 or 1500 mg TiO_2/kg bw. Dimethylbenzanthracene (12.5 mg/kg in corn oil) was used as the positive control. Twenty-four hours after the final dose, bone marrow and peripheral blood erythrocytes were analyzed for MN in the first experiment and bone marrow erythrocytes were analyzed in the second experiment. Health Canada's Food Directorate considered the results of this study as negative because the elevated test results at the 1000 mg/kg bw/d dose level (that is, 3.50 and 3.60 micronuclei per 1000 PCEs for experiments 1 and 2, respectively) were within the range of control data for the same sex and strain reported by the same authors (that is, 1.10 to 3.70 micronuclei per 1000 PCEs) (Health Canada 2022b). Shelby and Witt (1995) also tested chromosomal aberration in bone marrow after male mice (n = 8/group) were administered the same form of titanium dioxide as Shelby et al. (1993). A single i.p. injection was given at 625, 1250, or 2500 mg TiO_2/kg bw. Bone marrow was harvested 17 or 36 hours after the injection and analyzed for chromosomal aberration. Authors reported negative results for chromosomal aberration; however, the route of administration in these studies is not considered relevant to evaluate oral toxicity. Inconclusive results were reported by Sycheva et al. (2011) in a MN assay in bone marrow when male mice were exposed to a cosmetic grade titanium dioxide (anatase, 160 nm ± 59.4 nm determined by electron microscopy) through oral gavage at 40, 200 and 1000 mg/kg/day for 7 days. Bone marrow was removed 24-hours after the last

administration. EFSA (2021) reported negative results for bone marrow MN assay. Health Canada's Food Directorate considered the results of the bone marrow MN study as equivocal because the increase in micronuclei incidence was considered small in magnitude. In the study, forestomach and colon were also removed and epithelial cells were analysed for MN. However, cytotoxicity was reported in those epithelial cells; therefore, the results were not considered relevant. EFSA (2016) and Health Canada's Food Directorate (Health Canada 2022b) have identified several additional limitations of the study, including deviation of OECD TG 474 due to the use of fewer sample numbers (1 000 immature erythrocytes per animal instead of the 4 000 recommended) and the use of an inappropriate statistical test for the analysis of results. Another limitation was the lack of a positive control group in the study protocol. Inconclusive results were also reported for Donner et al. (2016) for MN in peripheral blood reticulocytes when male and female SD rats (n = 5/sex/dose) were given a single oral dose of titanium dioxide (anatase, 27% nanoparticles; hydrodynamic diameter 153 nm; determined by TEM) at 500, 1000 or 2000 mg TiO_2/kg bw by oral gavage. EFSA (2016) considered this study to be less reliable due to a lack of demonstration of systemic exposure.

The EFSA (2021) panel also assessed other studies, including markers of DNA damage, oxidized DNA bases, reactive oxygen species (ROS) generation, epigenetic DNA methylation, and cell transformation (EFSA 2021). After analyzing the body of evidence, the EFSA (2021) panel concluded that "TiO_2 particles had the potential to induce DNA strand breaks and chromosomal damage, but not gene mutations". The EFSA (2021) panel reported that multiple modes of action may operate in parallel for the genotoxicity of E171. There are uncertainties whether a threshold mode of action could be assumed. Similarly, after analyzing the physicochemical properties of titanium dioxide particles, the EFSA (2021) panel also stated that a cut-off value for particle size could not be established for genotoxicity. As a result, the EFSA (2021) panel concluded that "a concern for genotoxicity of TiO_2 particles that may be present in E171 cannot be ruled out".

Based on available key reviews (EFSA 2016 and 2021), titanium dioxide micro particles display mixed results for genotoxicity in *in vitro* and *in vivo* assays.

The UK independent Government Committee on Mutagenicity (COM) reported that the limitations of the current data used to characterize genotoxicity, such as mixed particle size, wide variety of testing approaches, did not support a definitive conclusion. Thus, COM did not agree with the EFSA overall conclusions on the genotoxicity of E171 (COT 2022).

Recently, Kirkland et al. (2022) published a review paper on 'a weight of evidence review of the genotoxicity of titanium dioxide'. The authors conducted a comprehensive weight of evidence (WoE) assessment of the genotoxicity of titanium dioxide using available data, including the genotoxicity studies considered in the EFSA (2021) assessment. The studies that met the reliability and quality criteria included both microscale and nanoscale titanium dioxide. Based on the analysis, authors determined

that the studies that reported positive results for genotoxicity were associated with high cytotoxicity, oxidative stress, inflammation, apoptosis or combination of all these effects. Authors also identified that titanium dioxide particle size did not correlate with genotoxic effects and the reproducibility of effects on the same endpoint was not evident from the available studies. As such, the authors acknowledged that the existing evidence does not support a direct DNA damaging mechanism for both nanoscale and microscale titanium dioxide (Kirkland et al. 2022).

Carcinogenicity and preneoplastic lesions in the GIT

The 2-year dietary study by NCI (1979) examined the carcinogenicity of titanium dioxide. In this study, F344 rats and B6C3F1 mice (50 animals/sex/dose) were fed anatase titanium dioxide (particle size range from 113 to 135 nm and 109 to 124 nm by SEM) in their diet at 0, 25 000 or 50 000 ppm daily for 103 weeks (NCI 1979). According to EFSA (2016), these dose levels were equivalent to 2 275 or 4 550 mg TiO_2/kg bw/day, respectively, for female rats and 2 025 or 4 050 mg TiO_2/kg bw/day, respectively, for male rats. The dose conversions for mice were 5 375 or 10 750 mg TiO_2/kg bw/day, respectively, for females and 4 225 or 8 450 mg TiO_2/kg bw/day, respectively, for males. Food consumption rate and body weights of adult male and female rats and mice were used to calculate the dose conversion. At 104 weeks, surviving animals were sacrificed and gross and microscopic pathology of major tissues, organs and lesions were evaluated. While white feces were noted due to the colour of the test material, there were no treatment-related adverse effects reported at any doses tested. A significant increase in mortality was observed in female mice exposed to the highest dose; however, this was not considered a treatment-related effect. The significant difference was likely due to a greater survival rate of female mice in the concurrent vehicle control group (Cameron et al. 1985; NSF 2005; Ramoju et al. 2020). The two-year dietary study in mice and rats did not report any significant incidence of tumors in treated animals compared to control animals. NCI (1979) determined that chronic exposure to titanium dioxide up to 50 000 ppm in the diet was not carcinogenic to Fisher rats and B6C3F1 mice. After analyzing the available data, IARC (2010) concluded that oral, subcutaneous, and intraperitoneal administration of titanium dioxide did not produce a significant increase in tumour frequency in rats or mice.

The EFSA (2021) also investigated the potential for tumour promoting effects with oral exposure to E171 based on the evidence presented in studies published after the EFSA publication in 2016.

Bettini et al. (2017) studied the formation of aberrant crypt foci (ACF) in the colon region of rats. It has been suggested that ACF is the earliest preneoplastic lesions in colorectal cancer progression. Male rats, treated with dimethylhydrazine (DMH) to initiate colon carcinogenesis, were exposed to E171 in drinking water at dose levels of 200 µg/kg bw/day and 10 mg/kg bw/day (a human representative dose) for 100 days. The particle size distribution of E171 ranged from 20 to 340 nm (D_{50} 118±53 nm), with 44.7% of particles <100 nm in diameter (Bettini et al. 2017). At the end of the treatment period,

animals were killed randomly, and the colon was coded to be used for aberrant crypts (ABCs) and ACF investigation. The number and the size of ACF and number of crypts per ACF were counted under a light microscope at 40X magnification in duplicate by two readers. The pathological analysis was conducted in a blinded manner. Based on this data, authors reported a significant increase in the total number of aberrant crypts per colon, and the number of large ACF per colon (that is, more than three aberrant crypts per ACF) at 10 mg/kg bw/day compared to untreated controls and 200 µg/kg bw/day groups. Authors also studied whether E171 exposure at 10 mg/kg bw/day would initiate spontaneous development of ACF in DMH untreated rats (n=11). In this portion of the experiment, four E171 treated rats developed lesions with 1 to 3 aberrant crypt(s) per ACF, and 1 rat developed a severe lesion of 12 aberrant crypts. Based on these results, the authors determined that E171 at 10 mg/kg bw/day promoted colon micro-inflammation and spontaneously generated pre-neoplastic lesions in the large intestine However, Bettini et al. (2017) suggested that the ACF promotional effect is likely due to the nanoscale titanium dioxide particles present in E171 food additives because similar *in vitro* effects were observed in the same study conducted using nanoscale titanium dioxide particles (that is, NM-105).

The observations of Bettini et al. (2017) could not be replicated in subsequent studies, such as REACH ([modified 2022]), with E171 administered via the oral route. An OECD TG 443 compliant EOGRT study (REACH [modified 2022]) included a satellite group of F0 male and female rats (n=10) to study the potential of ACF formation in the colon from E171 (EFSA 2021). In this portion of the study, rats were exposed to E171 at doses of 0, 100, 300 or 1 000 mg/kg bw/day in the diet over 122 days (study duration reported in REACH [modified 2022]). As ACF examination is not within standard methodology, this portion of the study was not a requirement in OECD TG 443. For histopathological analysis, the entire surface of the colon was examined in a blinded manner for ACF and aberrant crypts. Pathology examination was performed in accordance with OECD TG 443. Mild morphological variability of crypts was observed in 7 treated animals out of total animals used in the study (males: 1/10, 0/10, 1/10, 1/10; females: 1/10, 0/10, 1/10, 2/10 in the control, low-, mid- and high-dose groups, respectively). However, the authors determined that these changes were inconsistent with the appearance and the definition of ACF given in Shwter et al. (2016) (that is, foci containing more than two aberrant crypts). According to this study, oral exposure to E171 at doses up to 1 000 mg/kg bw/day did not induce ACF in the colon. Of note, this study did not include a positive control group with a known tumour initiator, such as DMH to compare with ACF formation from E171 treatment. Similarly, Han et al. (2020) who administered sonicated E171 via gavage for 90 days to rats, did not report lesions in the stomach or colon of treated animals.

Blevins et al. (2019) also investigated ACF or aberrant crypt in male rats (n=15) exposed to E171 alone (anatase, 110 to 115 nm, 36% nanoscale particles, analyzed by SEM) via diet up to 267 mg/kg bw/day for 100 days. However, pathological examination of colon samples was limited to a small area due to a technical issue related to tissue fixation (Blevins et al. 2019). Because of this limitation, the EFSA (2021) panel could not

infer the potential for ABC and ACF formation based on this study. A detailed analysis of ACF formation in the GIT and its use as a potential biomarker of colorectal cancer can be found in EFSA (2021) and the State of the Science published by Health Canada's Food Directorate (2022b).

On the basis of the key available data and reviews (NCI 1979; IARC 2010; OECD 2013; EFSA 2021), the weight of evidence suggests that there are no carcinogenicity concerns associated with oral exposure to titanium dioxide microparticles in experimental animals. The EFSA (2021) considered that food grade titanium dioxide, E171 may induce ACF in male rats based on the findings reported by Bettini et al. (2017), which may indicate a tumour-promoting ability for E171. However, ACF formation associated with titanium dioxide exposure reported by Bettini et al. (2017) was not observed in any other previous or subsequent studies (for example, NCI, 1979; Han et al. 2020; REACH [modified 2022]). Health Canada's Food Directorate also noted that there was no consistent evidence of preneoplastic lesions, including ACF, in the colons of rodents exposed to food-grade titanium dioxide via the oral route (Health Canada 2022b).

Chronic human data:

Some epidemiological studies have reported "yellow nail syndrome" due to titanium accumulation in fingernails in individuals who have been chronically exposed to elevated levels of titanium predominantly from medical interventions (Kim et al. 2019). These studies have limited use in risk assessment, mainly due to insufficient data to establish a dose-response relationship and insufficient consideration of confounding factors.

Based on available key data and reviews (NCI 1979; IARC 2010; OECD 2013; EFSA 2021; REACH [modified 2022]), microscale titanium displays low chronic/repeated dose toxicity in experimental animals and humans.

Selection of critical study and the point of departure (POD) for oral exposure to titanium:

Previously, international assessments, such as NSF (2005) have considered the highest dose tested in the NCI (1979) study as the critical POD to derive guidance values. However, since the publication of the NCI study and NSF review, a robust, GLP and OECD guideline compliant EOGRT study (REACH [modified 2022]) has become available. The EOGRT study examined several key endpoints including developmental and reproductive effects, developmental neurotoxicity, immunotoxicity and formation of ACF. A NOAEL of 623 mg Ti/kg bw/day (1 000 mg TiO_2/kg bw/day), which is the highest dose tested in the EOGRT study (REACH [modified 2022]), was selected as a suitable POD for the risk characterization of oral exposure to microscale forms of the 13 titanium-containing substances in this human health assessment. In the absence of toxicity data on the other titanium-containing substances, the POD from titanium dioxide

was used as a surrogate for the group. Several other oral sub-chronic studies in experimental animals exposed up to a dose of 1 000 mg/kg bw/day titanium dioxide (either pigment-grade or food-grade) also did not indicate adverse effects (Warheit et al. 2015a, 2015b; Han et al. 2020).

5.1.2.1 Derivation of the biomonitoring equivalent (BE)

In BE derivation, an internal concentration or range of concentrations of a chemical or its metabolites in a biological medium (for example, blood, urine, or other media) that is consistent with an existing health-based guidance value such as a RfD or a tolerable daily intake is derived using available kinetic data or by conducting regression analysis between exposure and blood or urine concentrations (Hays et al. 2008, 2016).

The steady-state titanium whole blood BE for the critical POD from the EOGRT study was derived using the physiologically-based pharmacokinetic model (PBPK) explained in Ramoju et al. (2020). This model was based on a published pharmacokinetic model by Heringa et al. (2016). The Heringa et al. (2016) model was based on kinetic data from Geraets et al. (2014), and the authors assumed that kinetic parameters from intravenous dosing are similar to oral exposure. In Geraets et al. (2014), Wistar rats were administered various particle sizes of titanium dioxide intravenously (NM-100, NM-102, NM-103 and NM-104; mean particle size in the range of 67 to 267 nm) (injected dose of 5 mg/kg bw) or through oral gavage (NM-101; NM-102; NM-103 and NM-104; mean particle size in the range of 38 to 186 nm) (administered doses for males and females were 6.8 to 8.5 and 10.9 to 12.0 mg TiO_2/kg bw/day, respectively) for five consecutive days. The treatment period was followed by an observation period of up to 90 days. Tissue samples were collected to analyze titanium concentrations at days 6, 14, 30 and 90 for rats exposed to titanium dioxide through intravenous injection. For rats orally exposed to titanium dioxide, tissue analysis was only performed on day 6.

The model was developed using the key findings from the Geraets et al. (2014) study and incorporated the weight-of-evidence from other animal and human oral studies. Those key findings included: 1) 0.02% of titanium was orally absorbed; 2) blood titanium levels were distributed from blood to tissues over several days, leading to accumulation in various tissues; 3) the highest concentration of titanium was measured in the liver and spleen; 4) aside from liver (fecal elimination), very low or negligible elimination occurred via other routes; and 5) at the end of the observational period, 55% to 80% of the total distributed dose was found in the tissues analyzed in the study (that is, blood, liver, spleen, lung, kidney, heart, brain, thymus, and testes/ovaries) (Ramoju et al. 2020). Thus, the multi-compartmental PBPK model consists of compartments specifically for the blood, liver, spleen, gonads and a single compartment to represent the “rest of the body” (see Appendix C, Figure C-1). Details on the PBPK model are available in Ramoju et al. (2020).

A sensitivity analysis identified oral absorption rate as the most sensitive model parameter. Oral absorption had a sensitivity coefficient of 1 (that is, oral absorption rate

and estimated titanium accumulation in tissues are directly proportional). Model validation was conducted using the oral exposure dataset found in Geraets et al. (2014). Based on the model validation results, it was determined that the model overestimated the concentration of titanium in the liver by a factor of 1.5 to 4, which is within the range of liver concentration values reported in the published literature (Ramoju et al. 2020).

This model facilitates the calculation of internal concentrations (that is, blood and tissue concentrations) of titanium after oral ingestion (Heringa et al. 2016; Ramoju et al. 2020). Thus, in the BE derivation, the model was used to simulate the concentration of titanium in whole blood. The model assumed that titanium particles were uniformly distributed across all components in the blood (that is, plasma, erythrocytes, serum, etc.) (Heringa et al. 2016; Ramoju et al. 2020).

Ramoju et al. (2020) derived a BE value of 28 µg/L for the RfD established by the NSF, which was based on the NOAEL from NCI (1979) study and the application of UFs (that is, x10 inter-species extrapolation, x10 for intra-species variability, and x10 for database deficiency). The additional UF of 10 for database deficiency was to account for the lack of a one-generation reproductive toxicity study.

A new BE was derived for male and female rats using the NOAEL of 623 mg Ti/kg bw/day for this human health assessment, the highest dose tested in the EOGRT study (REACH [modified 2022]). The model code for titanium pharmacokinetics in the rats after oral administration was obtained from the supplementary data to Ramoju et al. (2020) to derive a steady-state whole blood BE value. The PBPK model was simulated for the POD for both parental (F0) and F1 generation for chronic steady-state scenarios. The model was run in the Berkeley Madonna platform, with starting age of 71 days for the parental generation and 21 days for the F1 generation. The starting age is essential to ensure the model estimates include increased food consumption with age. According to the model simulation for chronic exposure, the approximate steady-state blood concentrations of titanium associated with the NOAEL (BE_{POD}) for male and female rats were 2.15 and 1.61 mg/L, respectively. Following the application of UFs of 2.5 for inter-species toxicodynamic variation and 10 for intra-species variation, the BE values for male and female rats were 86 and 65 µg/L, respectively. The UF for inter-species toxicokinetic variation was not considered as it was already accounted for in the PBPK model. As a conservative approach, the lowest BE of 65 µg/L for female rats was brought forward for the risk characterization of systemic exposure. The BE derivation steps are presented in the Table C-1 of Appendix C.

5.1.3 Health effects of dermal exposure to titanium

Based on available data and reviews, titanium dioxide poses low acute, short-term, and chronic toxicity via the dermal route of exposure as microscale titanium dioxide cannot penetrate beyond the outermost layer of viable skin (NCI 1979; Lademann et al. 1999; Sadrieh et al. 2010; OECD 2013; NICNAS 2016).

Several carcinogenicity studies are available on rats and mice exposed to titanium dioxide via the dermal route (CLH 2016). These studies provided negative results for carcinogenicity; however, they were conducted using nanoscale titanium dioxide particles (CLH 2016) and therefore were not considered further in this human health assessment.

Based on available key reviews and studies (Lademann et al. 1999; Sadrieh et al. 2010; CLH 2016; ECHA 2017), titanium displays no adverse effects via the dermal route of exposure due to low dermal absorption of the substance.

5.1.4 Health effects of inhalation exposure to titanium

In the absence of inhalation toxicity data for the majority of the titanium-containing substances in this group, inhalation toxicity data for titanium dioxide was used as surrogate data for the health effects assessment for the Titanium-containing Substances Group.

Acute exposure:

A limit test conducted according to OECD TG 403, cited in REACH ([modified 2022]), was available to assess acute inhalation exposure to titanium dioxide. Male and female SD rats (5/sex/dose) were exposed by nose-only for 4 hours to titanium dioxide, either at measured concentrations of 3.43 mg/L (3 430 mg TiO_2/m^3) (MMAD 3.2 µm) or 5.09 mg/L (5 090 mg TiO_2/m^3) (MMAD 7 µm). The animals were followed up for 14 days. Over the 14-day post-exposure observation period, no mortality, body weight changes or adverse clinical signs were reported for any of the exposure concentrations.

Based on available key data (REACH [modified 2022]), titanium displays low acute toxicity via the inhalation route.

Short-term toxicity:

In a study conducted by Warheit et al. (1997), CD male rats were administered titanium dioxide dust via whole-body inhalation for 6 hours/day, 5 days/week, for four weeks at 5, 50 or 250 mg TiO_2/m^3 (MMADs of 1.9, 1.7, or 1.4 µm, respectively) and observed for 6 months post-exposure. Animals were evaluated by bronchoalveolar lavage fluid (BALF) analysis, clearance analysis, *in vitro* macrophage function, and histopathology at 0 hours, 1 week, and 1-, 3-, and 6-months post-exposure. The mid- and high-dose animals showed a wide spectrum of effects within the lungs; and while the types of lesions were similar in both doses, the severity was significantly higher at the highest dose. Four-week exposures to 250 mg TiO_2/m^3 produced a persistent inflammation and macrophage aggregation, which was sustained through a 3-month post-exposure period and was still visible at 6 months post-exposure. No effects were reported at 5 mg TiO_2/m^3; thus, this dose is considered as the no-observed-adverse-effects-concentration (NOAEC).

In another study by Henderson et al. (1995) as cited in NIOSH (2011) and OECD (2013), female rats were exposed to titanium dioxide (rutile; MMAD 1.3 µm) via nose-only at concentrations of 0, 0.1, 1.0, or 10 mg TiO_2/m^3 6 hours/day, 5 days/week for 4 weeks followed by a 24-week observation period. There were no changes in the BALF or any histopathological changes. Therefore, the OECD (2013) established 10 mg TiO_2/m^3 (6.0 mg Ti/ m^3) as the NOAEC.

Bermudez et al. (2002) examined the effects of inhaled rutile titanium dioxide (MMAD of 1.4 µm) in female rats, mice and hamsters in a 13-week study. Animals (65, 73 and 73 animals/dose for rats, mice and hamsters, respectively) were exposed to 0, 10, 50 or 250 mg TiO_2/m^3 pigmentary titanium dioxide via whole-body inhalation for 6 hours/day, 5 days/week over 13 weeks, with recovery groups held for an additional 4, 13, 26 or 52 weeks (46 weeks for hamster study), respectively, post-exposure. At each point, animals were studied for lung burden and a variety of pulmonary parameters, including inflammation, cytotoxicity, lung cell proliferation and histopathological alterations. Both rats and mice showed a significant impairment for alveolar macrophage-mediated clearance at the exposure levels of 50 and 250 mg TiO_2/m^3, leading to pulmonary overload. Hamsters were able to clear titanium dioxide particles better than the other two species. Inflammation as indicated by an increase in macrophage, neutrophil, total protein, and lactate dehydrogenase in BALF, was reported at 50 and 250 mg/m^3 in all three species. In hamsters, the inflammation markers were only significantly elevated at the highest dose level compared to control animals (Bermudez et al. 2002). Inflammation was more severe in rats than mice and hamsters. In mice and rats, inflammation was observed throughout the post-exposure recovery period whereas in hamsters, inflammation eventually disappeared due to rapid clearance. Histopathological observation showed alveolar hypertrophy and hyperplasia in Type II epithelial cells at 50 and 250 mg/m^3 in rats after 13 weeks of exposure. In addition, at 250 mg TiO_2/m^3, rats also showed alveolar metaplasia, which was not seen in mice or hamsters. Observation of alveolar hypertrophy and hyperplasia in Type II epithelial cells was minimal in hamsters. The OECD (2013) considered the NOAEC in this study as 10 mg TiO_2/m^3 (6.0 mg Ti/m^3) for all the species tested.

Other authors, such as Everitt et al. (2000) and Reverdy et al. (2000), also reported similar findings as Bermudez et al. (2002) when rats, mice and hamsters were exposed to the same dose levels of titanium dioxide microparticles for 13 weeks.

In another study, Thyssen et al. (1978) exposed male and female rats (50/sex) to 16 mg TiO_2/m^3 (0.5 µm) for 6 hours/day, 5 days/week for 12 weeks and animals were observed until spontaneous death. Exposed animals did not show any treatment-related change in clinical observations, body weight or carcinogenicity (Thyssen et al. 1978).

Genotoxicity:

Based on the decision of EFSA (2016) and ECHA (2017) and analysis of available studies, the SCCS (2020) determined that if exposure occurs through inhalation,

titanium dioxide could exert genotoxic effects in the lungs. The genotoxicity is likely due to indirect mechanisms, such as oxidative stress or secondary mechanisms by chronic alveolar inflammation due impaired macrophages after the development of lung overload (Driscoll et al. 1997; CLH 2016; SCCS 2020). Thus, lung overload would be required prior to the development of genotoxicity. This mechanism of action is associated with any type of small particle rather than a characteristic of titanium in particular.

Chronic toxicity and carcinogenicity:

In 2006, the IARC concluded that for titanium dioxide there was sufficient evidence of carcinogenicity via the inhalation route in experimental animals and inadequate evidence of carcinogenicity in humans (Group 2B – “possibly carcinogenic to humans”) (CAS RNs 13463-67-7, 1317-70-0, and 1317-80-2) (IARC 2010). The German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area has classified the respirable fraction of titanium dioxide as a category 4 carcinogen (Hartwig 2020).

The IARC (2010) assessment considered that the classifications apply to both nanoscale and microscale titanium dioxide particles. The supporting studies for carcinogenicity classifications are summarized below. It should be noted that the lung tumours were only reported at dose levels that caused lung overload in inhalation animal bioassays for titanium dioxide. Additionally, the exposure levels at which the tumors were reported in the microscale titanium dioxide study (Lee et al. 1985) exceeded the maximum tolerable dose. In contrast to IARC classification, the National Industrial Chemicals Notification and Assessment Scheme of Australia (NICNAS) recommended that the substance does not require classification and labelling (NICNAS 2016). The NICNAS (2016) conclusion was reached based on several different criteria, including sufficient ongoing risk management measures in place, lack of genotoxicity, and observation of lung overload in rats prior to tumor development.

The carcinogenicity classifications for titanium dioxide were based on three chronic inhalation studies in animals using microscale titanium dioxide (Lee et al. 1985 and Muhle et al. 1991) and nanoscale particles (Heinrich et al. 1995). In addition, epidemiological studies have been reviewed in the IARC and NIOSH assessments and did not find adequate evidence for carcinogenicity in humans (IARC 2010; NIOSH 2011). The key animal studies are summarised below.

Lee et al. (1985) exposed groups of male and female Crl:CD rats (50 animals/sex/dose) via inhalation to a rutile titanium dioxide (MMAD 1.5–1.7 µm) at concentrations of 0, 10, 50 or 250 mg TiO_2/m^3 using whole-body inhalation for 6 hours/day, 5 days/week over 2 years. None of the exposed groups showed treatment-related abnormal clinical signs, body weight changes or excess of morbidity or mortality compared to the untreated control group. Increased incidences of pneumonia, tracheitis and rhinitis with squamous metaplasia of the anterior nasal cavity were reported in both males and females in all

treatment groups. The severity of the lesions was dose-dependent and was minimal at 10 mg TiO_2/m^3. The authors determined that the effects at 10 mg TiO_2/m^3 met the biological criteria for a “nuisance dust” and that those effects were mild and reversible. At doses of 50 mg TiO_2/m^3 and higher, there was a significant increase in lung and thymus weights. Animals in these treatment groups also showed alveolar proteinosis, bronchiolarization of alveoli, and fibrosis. While no significant increase in lung tumours was reported at 10 or 50 mg TiO_2/m^3, bronchioalveolar adenomas (benign lung tumors) were reported in both sexes at 250 mg TiO_2/m^3. These tumours were considered secondary to lung overload in the test animals and are not specific to titanium exposures below this threshold (NICNAS 2016; Thompson et al. 2016; ECHA 2017). Animals also showed non-neoplastic cysts. No carcinomas were reported in this study. Based on the treatment-related lung effects (that is, tracheitis, rhinitis with squamous metaplasia of the anterior nasal cavity, alveolar cell hyperplasia and broncho/bronchiolar pneumonia), 10 mg/m^3 (6.0 mg Ti/m^3) is considered as the lowest-observed-adverse-effects concentration (LOAEC).

Muhle et al. (1991) administered titanium dioxide (MMAD 1.1 µm) at 0 or 5 mg TiO_2/m^3 for 6 hours/day, 5 days/week for 24 months by whole-body inhalation to rats (50 rats/sex/dose). No significant difference in lung tumours were observed in exposed animals. A 5% incidence of lung fibrosis, minor changes in the cytologic pattern of BALF and lymphoid hyperplasia of lung-associated lymph nodes were noted in exposed animals. However, this study was designed to test a single concentration of titanium dioxide as a positive control for a study testing carcinogenicity of inhalation exposure to toner. As only a single concentration was tested, and study design did not follow any test guidelines, this study was not considered sufficiently robust to derive a critical POD for chronic exposure to titanium.

Another study considered in the IARC (2010) classification was a chronic rat and mice study conducted by Heinrich et al. (1995) using ultrafine (nanoscale) titanium dioxide particles. While studies conducted on nanoparticles were not relevant to this human health assessment, the details of this study were included here because it is one of the key lines of evidence used by IARC (2010) for its cancer classification. The female Wistar rats and female Crl:NMRI BR mice (100 animals/dose) were exposed by whole-body inhalation to TiO_2 (primary particle size 15–40 nm) at an average air concentration of 10 mg TiO_2/m^3 for 18 hours/day, 5 days/week, (for both species, as cited in NIOSH 2011) over 24 and 13.5 months, respectively. Following cessation of dosing, animals were maintained in clean air for recovery (6-month period for rats and 9.5-month period for mice). Benign keratinizing cystic squamous-cell tumors, adenoma, adenocarcinomas and squamous cell carcinomas were observed at 10 mg/m^3 in exposed rats. The total number of lung tumours was significantly different in exposed rats compared to control animals. However, mice did not show a significantly increased incidence of lung tumours. Since only a single concentration of titanium dioxide nanoparticles was used, this study was not considered further in this human health assessment. It should also be noted that studies have shown that ultrafine (nanoscale) particles produce more severe

pulmonary effects in rats, including lung carcinomas, than an equal mass of microscale particles (NIOSH 2011; Thompson et al. 2016; ECHA 2017).

Rats exposed to concentrations of 50 mg TiO_2/m^3 and above in Lee et al. (1985) had impaired lung clearance pathways due to pulmonary overload (Warheit and Frame 2006; IARC 2010; NIOSH 2011; NICNAS 2016; ECHA 2017; Kawasaki 2017). Other authors have concluded that the rat model is more sensitive to titanium dioxide-induced lung effects than other rodent models, including mice and hamsters and non-human primate models (monkeys) (Krombach et al. 1997; Bermudez et al. 2002; Warheit and Frame 2006). Thus, the lung tumours reported in rats exposed to high concentrations of titanium dioxide microscale particles in Lee et al. (1985) were not considered to be relevant specifically for exposure to titanium by the general population as tumours only occurred at concentrations that caused lung overload (that is, 250 mg TiO_2/m^3) (Warheit and Frame 2006; NIOSH 2011; Kawasaki 2017). This is consistent with the Committee for Risk Assessment opinion on the proposed harmonized classification and labelling of TiO_2 (ECHA 2017). The report states that complete cessation of alveolar clearance occurred at 50 mg TiO_2/m^3 and above in Lee et al. (1985), which is consistent with an observation of pulmonary overload (ECHA 2017). A similar outcome was reached in a comprehensive review by Thompson et al. (2016). The authors agreed that particle overload is a well-accepted concept for fine (microscale) titanium dioxide particles. The authors further explained that the mechanism of toxicity induced by ultrafine (nanoscale) particles is not well understood (Thompson et al. 2016).

A recent review by Bevan et al. (2018) explored the issue of lung overload and lung cancer associated with toxicity testing of poorly soluble particles, such as titanium dioxide, carbon black, talc and toner particles in rodents. They determined that, while the evidence suggests that the rat lung model is unreliable as a predictor for human lung cancer risk associated with these substances, it is a sensitive model for detecting various threshold inflammatory markers, with utility for use in non-neoplastic risk assessment. A similar decision was provided by ECETOC (2013) and Warheit et al. (2016).

Thus, the inflammatory response noted in animals at 10 mg TiO_2/m^3 (6.0 mg Ti/m^3) in Lee et al. (1985) was considered the critical effect for chronic risk characterization. The titanium dioxide concentration at the LOAEC (that is,10 mg TiO_2/m^3) was converted to a titanium concentration using titanium and titanium dioxide molecular weights (10 mg TiO_2/m^3 x (47.87 g/mol / 79.87 g/mol) = 6.0 mg Ti/m^3) to be applicable to all titanium-containing substances in the group. The LOAEC of 6.0 mg Ti/m^3 was derived from a study in which animals were exposed on an intermittent basis (6 hours per day, 5 days a week). The LOAEC of 6.0 mg Ti/m^3 was further adjusted to represent continuous exposure concentration by multiplying the number of hours per day (6/24) and the number of days per week (5/7) titanium dioxide was administered to test animals. This adjustment was conducted according to the United States Environmental Protection Agency guidance on inhalation risk assessment (US EPA 1994, 2009). The adjusted LOAEC for non-cancer effects is 1.1 mg Ti/m^3. This adjustment is considered

appropriate when the available toxicokinetic data indicate that titanium particles deposited in lungs can accumulate over time due to slow clearance, which could lead to time-related enhanced lung effects.

Human data:

Several epidemiological studies reported a correlation between environmental titanium exposure during pregnancy and low birth weight (Bell et al. 2012; Basu et al. 2014; Jin et al. 2021). However, these effects were reported at air concentrations several-fold higher than the average exposure levels from air concentrations reported for the general population.

Epidemiology studies that examined titanium dioxide inhalation exposure in occupational settings have not shown clear evidence of lung overload or carcinogenicity in workers (IARC 2010; NIOSH 2011; ECETOC 2013; ECHA 2017). While several international agencies, such as OSHA (2002), ACGIH (2009) and NIOSH (2011), have derived exposure guidance values for workers, no such guidance values are developed for titanium dioxide inhalation exposure in the general population.

These epidemiological studies were limited by various shortcomings, such as small sample sizes, imprecise or absent exposure assessment and insufficient consideration of confounding factors. As a result, the critical POD for this human health assessment was not based on available epidemiological studies, but those studies were used as supporting evidence for the health effects assessment.

Summary of hazard data for inhalation exposure

In the absence of inhalation toxicity data for most titanium-containing substances in the group, inhalation toxicity data for titanium dioxide was used as surrogate data for the health effects assessment of the group.

Overall, microscale titanium (as titanium dioxide) inhalation has been shown to produce portal-of-entry (lung tissue) effects in all species tested. In animal models (specifically the rat), failure to clear titanium dioxide particles from the lung leads to lung overload and subsequent cancer development (Bevan et al. 2018). In human studies, lung lesions are limited to inflammatory reactions or fibrosis (Bos et al. 2019). As the lung tumours noted in rats occur only at doses that cause lung overload (Lee et al. 1985), lung carcinogenicity associated with titanium dioxide exposure is not relevant to humans exposed to much lower concentrations. Several other authors have also reached similar decisions (Warheit and Frame 2006; ECETOC 2013; Bevan et al. 2018).

The LOAEC of 10 mg TiO_2/m^3 (6.0 mg Ti/m^3) based on treatment-related lung effects (that is, tracheitis, rhinitis with squamous metaplasia of the anterior nasal cavity, alveolar cell hyperplasia and broncho/bronchiolar pneumonia) in rats reported in Lee et al. (1985) was selected as the critical POD. For the risk characterization of chronic

inhalation exposure to titanium-containing substances in the general population, a continuous air concentration for titanium (that is, 1.1 mg Ti/m^3) was calculated from the critical POD.

5.1.5 Consideration of subpopulations who may have greater susceptibility

There are groups of individuals within the Canadian population who, due to greater susceptibility, may be more vulnerable to experiencing adverse health effects from exposure to substances. The health effects assessment took into consideration the potential for differences or increased susceptibility based on life stage (that is, developing fetus), age and sex. Available data for titanium consists of kinetic, acute, short-term, sub-chronic, chronic, reproductive and developmental, neurodevelopmental, immunotoxicity, genotoxicity and carcinogenicity data in experimental animals. The data used to characterize risk also includes epidemiological data from workers and pregnant women. The available kinetic and health effects data do not indicate any difference in kinetic parameters or susceptibility to titanium-induced health effects based on life stage, age or sex. These considerations were taken into account in the selection of the critical health effect for risk characterization.

5.2 Exposure assessment

There are numerous studies which have measured titanium in various media including blood, air, drinking water, soil, dust and products available to consumers. These studies provide concentrations of total titanium in these media, but not substance-specific concentration data. In this exposure assessment, total titanium data will be used as a surrogate for substance-specific exposure data. Data on total titanium are expected to be a conservative surrogate for the 13 titanium-containing substances considered in this assessment, as total titanium data for environmental media, food, drinking water and products would include naturally occurring titanium and contribution from titanium-containing substances beyond the 13 substances in this Group.

This exposure assessment focuses on the characterization of exposure to microscale form of substances in the Titanium-containing Substances Group. Nanomaterials containing titanium (particles 1 to 100 nm) that may be present in environmental media or products are not explicitly considered in the exposure scenarios of this assessment, but measured concentrations of total titanium in environmental media, food or human biomonitoring data could include titanium from these sources.

Titanium and its alloys are used in medical procedures, such as dental implants and hip replacements. The health effects related to these uses were not considered in this assessment.

5.2.1 Environmental media, food, and drinking water

Titanium is a naturally occurring element that is present in environmental media in Canada (Grunsky et al. 2012; NAPS 2015, 2016, 2017, 2018; Rasmussen 2017; WBEA 2019, 2020; CFIA 2020, [modified 2022]; Health Canada 2020b, 2020c, 2020d, 2020e, 2020f, 2020g, 2020h). Total titanium has been measured in drinking water distribution systems, soil, outdoor air, indoor air, personal air, household dust in Canada and infant formula (Appendix A, Table A-2).

Food is a major contributing source of exposure to titanium for the general population (Jin and Berlin 2015; Ramoji et al. 2020). Titanium is naturally occurring in the environment and thus may enter the food chain; however, it may also be present in foods through the use of titanium-containing food additives, in particular titanium dioxide, and from potential use of substances in the Titanium-containing Substances Group as components in the manufacture of food packaging materials (personal communication, email from the FD, Health Canada, to the ESRAB, Health Canada, dated March 13, 2018; unreferenced; Health Canada [modified 2021a]). Concentrations of titanium in food were not analyzed as part of Health Canada's Total Diet Study; however, Canadian occurrence data are available through various surveys conducted by the Canadian Food Inspection Agency (CFIA) (CFIA 2020, [modified 2022])[8]. Canadian survey results indicate that titanium is found in a wide variety of foods. Titanium concentrations in most foods are less than 0.5 ppm. Some samples of certain foods such as confectionary, gelatin products, baked goods and baking mixes, were found to contain higher concentrations of titanium. These foods contained titanium concentrations up to 25 ppm and are permitted to contain titanium-containing food additives. Other foods that reported higher concentrations of titanium were dried foods (for example, spices, dried teas, and baking powder); this is not unexpected given that titanium would be concentrated during the drying process. Occurrence data from Europe and the US were also available for comparison. The highest concentrations of titanium dioxide in foods in Europe, from its use as a food additive, were reported in chewing gum (mean 3 115 ppm), food supplements in solid, liquid, or chewable form (mean 14 438 ppm) and processed nuts (mean 3 775 ppm) (EFSA 2021). In a study of 89 foods purchased from grocery stores in the US, the highest concentrations of titanium per serving were detected in baking ingredients (up to 3 590 ppm), candies (up

[8] CFIA surveys include targeted surveys and those conducted as part of the National Chemical Residue Monitoring Program and Children's Food Project surveys.

to 2 080 ppm), chewing gum (up to 2 640 ppm), chocolate (1 250 ppm), products with white icing or powdered sugar topping (up to 2 420 ppm) and powdered products mixed into foods such as drink mixes (up to 1 690 ppm) (Weir et al. 2012).

Typical dietary intake of titanium ranged from 0.3 to 0.5 mg per day based on data in publications from 1963 to 1969 (Jin and Berlin 2015). More recently, dietary exposure to food-grade titanium dioxide (E171) was estimated by the EFSA in their 2021 re-evaluation of food additive titanium dioxide (EFSA 2021). The EFSA assessment was based on consumption data from 40 dietary surveys conducted in 23 European countries, and on data on mean food additive use levels in foods reported by industry (mean concentration of E171 in food) reported by European member states (“refined non-brand-loyal consumer scenario”), most of which was collected during an EFSA call for data in 2013 (EFSA 2013). The upper mean estimated dietary intake of E171 in the refined non-brand-loyal consumer scenario ranged from 2.8 mg TiO_2/kg bw/day (1.7 mg Ti/kg bw/day) in older adults over 65 years old to 6.9 mg TiO_2/kg bw/day (4.1 mg Ti/ kg bw/day) in children 3 to 9 years old (EFSA 2021). Dietary exposure to E171 was also modelled for the US population using intake data from the national diet and nutrition survey in the United Kingdom (UK) and titanium concentrations in foods from the UK and the US (Weir et al. 2012). Average daily intake of E171 was estimated as a range of 1 to 2 mg TiO_2/ kg bw/day (0.6 to 1.2 mg Ti/ kg bw/day) for children under 10 years old and between 0.2 to 0.7 mg TiO_2/ kg bw/day (0.1 and 0.4 mg Ti/kg bw/day) for other age groups in the US (Weir et al. 2012). In the same publication, average daily intake of E171 in the UK was estimated as a range of 2 to 3 mg TiO_2/ kg bw/day (1.2 to 1.8 mg Ti/kg bw/day) for children under 10 years old and 1 mg TiO_2/ kg bw/day (0.6 mg Ti/kg bw/day) for other age groups.

Titanium dioxide is permitted for use in Canada as a food additive in a variety of foods at levels consistent with Good Manufacturing Practice. The foods and levels of use in which titanium dioxide is permitted as a food additive in Canada were similar to the permitted food additive uses in Europe prior to removal of the authorisation to use titanium dioxide (E171) in foods in Europe by the European Commission in 2022 (EC 2022b). Further details on the use of titanium dioxide as a food additive in Canada can be found in the Health Canada Food Directorate’s State of the Science on Titanium Dioxide (Health Canada 2022b). While some foods that may contain low levels of titanium from its presence in the environment were not included in the EFSA assessment, monitoring data for foods sold in Canada indicate lower levels of titanium than those reported in the EFSA assessment. Therefore, exposure estimates for titanium dioxide reported by the EFSA are expected to be conservative estimates of dietary exposures for the general Canadian population. Upper mean exposure estimates of dietary intakes of E171 from the refined non-brand loyal consumer scenario generated by EFSA are used as representative dietary intakes for titanium for the Canadian general population (Appendix A, Table A-3).

Concentrations of titanium in traditional, subsistence or country foods and surface water consumed by certain Indigenous peoples were measured as part of the Eastern

Athabasca Regional Monitoring Program (EARMP), an environmental monitoring program in Northern Saskatchewan (EARMP 2021a; [modified 2021b]). Concentrations of titanium in fish, mammals, birds, and berries were measured in six communities in Northern Saskatchewan from 2011 to 2020. Data measured in samples from 2015 to 2020 were combined to generate representative concentrations [that is, average or 95% upper confidence level of the mean (UCLM)] in each food commodity using the approach presented in the EARMP human health risk assessment published in 2018 (CanNorth 2018). Concentrations of titanium ranged from 0.01 µg/g in lake whitefish flesh in Camsell Portage up to 1.2 µg/g in berries (bog cranberries and blueberries) in Stony Rapids (EARMP [modified 2021b]). Intake of titanium from the consumption of country foods in these six communities ranged from 5.5 x 10^{-5} mg/kg bw/day for adults in Camsell Portage to 2.4 x 10^{-3} mg/kg bw/day for 1-year old children in Stony Rapids (Appendix A, Table A-4). The estimated intake of titanium from the consumption of country foods is not representative of total daily dietary intake as it does not include contribution from supermarket foods that may be consumed daily by individuals in these communities. The highest estimated intake of 2.4 x 10^{-3} mg Ti/kg bw/day for 1 year old children in Stony Rapids is lower than the highest daily dietary intake of 4.1 mg/kg bw/day for the general Canadian population (Appendix A, Table A-3). Additionally, biomonitoring data from a study including the communities sampled in the EARMP in Northern Saskatchewan are available (see section 5.2.3) (Saskatchewan Ministry of Health 2019).

Titanium was measured in infant formula in Canada as a part of the CFIA's 2018–2019 Children's Food Project (CFIA 2020). Concentrations of titanium were measured in 52 samples of powdered dairy-based infant formula and 7 samples of powdered soy-based infant formulas purchased in the Ottawa, Ontario and Gatineau, Quebec region of Canada (CFIA 2020). The mean concentrations measured in powdered dairy-based infant formula and soy-based infant formulas were 3.0 x 10^{-1} and 3.2 x 10^{-1} mg Ti/kg, respectively (CFIA 2020). Assuming 9 g of dry formula is reconstituted with 60 mL of water, the mean concentrations of prepared dairy-based infant formula and soy-based infant formulas were 4.5 x 10^{-5} and 4.8 x 10^{-5} mg/mL, respectively (CFIA 2020; Mead Johnson & Company, LLC 2020a, 2020b). Assuming formula-fed infants 0 to 5 months old consume 826 mL of prepared infant formula per day, the average daily exposure to titanium from infant formula for this age group is estimated to be 6.3 x 10^{-3} mg Ti/kg bw/day (Health Canada 2018). The estimated average exposure to titanium from infant formula for formula-fed infants 6 to 11 months old is 4.0 x 10^{-3} mg/kg bw/day, assuming a consumption of 764 mL of prepared infant formula per day (Health Canada 2018) (Appendix A, Table A-5). The highest estimated intake of titanium by formula-fed infants of 6.3 x 10^{-3} mg/kg bw/day for infants 0 to 5 months old is lower than the highest estimated dietary intake of 4.1 mg/kg bw/day for children 4 to 8 years old.

No data on titanium concentrations in Canadian human milk were available from the Maternal Infant Research on Environmental Chemicals project or other sources; therefore, occurrence data on titanium in human milk were obtained from the scientific literature. Average concentrations of titanium in human milk were reported in studies in

the US, Austria, Ukraine, Poland, Czech Republic and Germany (Anderson 1992; Amarasiriwardena et al. 1997; Krachler et al. 2000; Wappelhorst et al. 2002; de Rezende Pinto and Almeida 2018). The arithmetic mean concentration of titanium in human milk from studies in the US was 2.40 x 10^{-4} mg Ti/mL (Anderson 1992; Amarasiriwardena et al. 1997).The arithmetic mean concentration from available studies conducted in the US was used to estimate exposure to titanium from human milk in Canada as it was considered the most representative. Assuming exclusively human milk-fed 0- to 5-month-old infants consume 744 mL of human milk per day, average exposure to titanium from human milk was estimated to be 2.8 x 10^{-2} mg/kg bw/day (Appendix A, Table A-5).

Titanium may be present in drinking water in Canada from natural and anthropogenic sources. Titanium concentrations in drinking water internationally are generally low, between 5.0 x 10^{-4} and 1.5 x 10^{-2} mg/L (IPCS 1982). There is no health-based drinking water guideline or aesthetic objective for titanium in Canada. Canadian drinking water was analyzed for titanium in a national drinking water survey (Tugulea 2016). Titanium was not detected at or above the detection limit of 5.0 x 10^{-3} mg/L in all samples from distribution systems (n=97) (Tugulea 2016). As a conservative assumption, to estimate daily intake the concentration of titanium in drinking water in Canada is assumed to be equal to the limit of detection of 5.0 x 10^{-3} mg/L from the national drinking water survey data (Appendix A, Table A-5).

Concentrations of titanium in soil throughout Canada are expected to vary based on geology and anthropogenic inputs. Average concentration of titanium in soil globally is 0.33 weight percent (Woodruff et al. 2017). The percentage of titanium by weight in soil in the US range from 0.007% to 2% with an average of 0.29%. Titanium concentrations from 483 soil samples collected across Ontario in 1991 ranged from 758 to 7 420 mg/kg, with a median concentration of 3 070 mg/kg (Ontario [modified 2015]). The median titanium concentration in Ontario is within the range reported across the US. Soil in areas in close proximity to industrial facilities and point sources of titanium release may be elevated compared to median national levels due to atmospheric fallout (IPCS 1982; Woodruff et al. 2017). The median titanium concentration in Ontario of 3 070 mg/kg is used to estimate daily intake from environmental media (Appendix A, Table A-5).

Titanium was measured in studies of indoor air, outdoor air, personal air and household dust. Airborne titanium in particulate matter (PM) can originate from natural and anthropogenic sources. In 2015, total titanium was measured in 969 samples from 15 different sites across Canada as part of the National Air Pollution Surveillance (NAPS) Program. The median concentration of titanium particles of aerodynamic diameter less than or equal to 2.5 µm ($PM_{2.5}$) in outdoor air was 8.7 x 10^{-7} mg/m^3 (NAPS 2015). The median concentration of titanium in ambient air measured at over eight NAPS stations from 2016 to 2018 ranged from 1.3 x 10^{-6} to 1.7 x 10^{-6} mg/m^3 (NAPS 2016, 2017, 2018). Matched indoor, outdoor, and personal monitoring air data ($PM_{2.5}$ samples) were collected from Windsor, Ontario, in the years 2005 to 2006 (Rasmussen 2017). The

highest median titanium concentration in this study was measured in outdoor air (2.6 x 10^{-6} mg/m^3) followed by personal air (1.7 x 10^{-6}mg/m^3) and indoor air (1.4 x 10^{-6} mg/m^3) (Rasmussen 2017). Titanium was measured in various studies of Canadian outdoor air quality conducted by Health Canada between 2009 and 2013. Median $PM_{2.5}$ titanium concentrations ranged from 4.2 x 10^{-7} to 3.5 x 10^{-6} mg/m^3 (Health Canada 2020b, 2020c, 2020d, 2020e, 2020f, 2020g). Furthermore, titanium concentrations in various studies of Canadian indoor air quality conducted by Health Canada between 2009 and 2013 found median $PM_{2.5}$ titanium concentrations from 7.2 x 10^{-7} to 5.5 x 10^{-6} mg/m^3 (Health Canada 2020b, 2020d, 2020g). Within studies by Health Canada, indoor and outdoor air concentration measurements were conducted in the vicinity of schools, in transit environments, in residential areas and in areas in the vicinity of industrial facilities. Titanium is present and detected in Canadian urban house dust and was detected in all homes studied (n=1025) with a median concentration of 2 100 µg/g (Rasmussen 2017). The median indoor (1.4 x 10^{-6} mg/m^3) and outdoor (2.6 x 10^{-6} mg/m^3) air concentrations measured in Windsor, Ontario, and the median concentration of titanium in Canadian house dust (2 100 µg/g) were used to estimate daily intake from environmental media.

Areas in close proximity to point sources of titanium release (for example, a mine, smelter or certain industrial manufacturing or processing facility) may have elevated levels of titanium in environmental media (Jin and Berlin 2015; Woodruff et al. 2017). Releases of titanium are not reportable to the NPRI; therefore, a complete list of sectors releasing titanium in Canada could not be identified, however certain sectors using titanium have been identified in the literature. In 2017, Rio Tinto Fer et Titane reported air emissions of 354 tonnes of total PM per year from their titanium ore mining facility located near Havre-Saint-Pierre, Québec and 1 254 tonnes of total PM from their associated metallurgical complex located near Sorel-Tracy, Québec (NPRI [modified 2022]). Titanium is a component of total PM released from the industrial facilities, but in the absence of data on the speciation of PM from the titanium industry in Canada the releases of titanium to air from the titanium industry in Québec could not be quantified. Iron and steel mills and the ferroalloy manufacturing industry (NAICS code 331110) are potential point sources of titanium release to air due to the use of titanium in the production of steel alloys. Maximum point of impingement titanium dioxide concentrations was modelled by ArcelorMittal Dofasco, a large Canadian steel mill located in Hamilton, Ontario as a requirement of Ontario Regulation (O.Reg. 419/05) (ArcelorMittal Dofasco 2018, 2019, 2020). Between the operating years of 2017 to 2019, the modelled maximum point of impingement titanium dioxide concentrations ranged from 3.8 x 10^{-4} to 6.6 x 10^{-4} mg TiO_2/m^3, equal to 2.3 x 10^{-4} to 4.0 x 10^{-4} mg Ti/m^3, respectively. Additionally, Heath Canada conducted air monitoring studies in areas in proximity to industrial facilities including near a steel mill in Sault Ste. Marie, Ontario (n=105), near a shale gas plant in Penobsquis, New Brunswick (n=55) and near a port in Halifax, Nova Scotia (n=512) (Health Canada 2020c, 2020e, 2020f). The median titanium $PM_{2.5}$ air concentrations in these studies ranged from 7.3 x 10^{-8} to 3.5 x 10^{-6} mg Ti/m^3 (Health Canada 2020c, 2020e, 2020f). Furthermore, the median concentrations of titanium in $PM_{2.5}$ samples from monitoring sites in the vicinity of oil

sands in Northeastern Alberta were between 7.8 x 10^{-7} and 2.0 x 10^{-6} mg/m^3 (n=230) in 2018 and between 8.1 x 10^{-7} and 2.2 x 10^{-6} mg/m^3 (n=302) in 2019 (WBEA 2019, 2020). Airborne titanium concentrations up to 1 x 10^{-3} mg/m^3 have been reported through air monitoring in industrialized areas in the US (IPCS 1982; Jin and Berlin 2015; Woodruff et al. 2017). The air concentration reported for industrialized areas in the US was used as surrogate data to estimate inhalation exposure to ambient air with point source influence. There is uncertainty if the titanium air concentration in proximity to titanium ore mining and refining facilities are higher than the air concentration in industrial areas in the US.

In studies conducted by Health Canada, titanium was measured in $PM_{2.5}$ samples from environments that may have elevated concentrations of PM compared to baseline ambient air including public transit, personal vehicles, and schools. Titanium was measured in samples of $PM_{2.5}$ from subways, buses, and private cars in large Canadian cities as part of Health Canada's urban transport exposure study conducted in Montreal, Ottawa, Toronto, and Vancouver (Health Canada 2020h). The median titanium air concentrations on subways (4.5 x 10^{-6} to 1.8 x 10^{-5} mg/m^3) and buses (6.0 x 10^{-6} to 8.0 x 10^{-6} mg/m^3) were higher than average indoor and outdoor titanium air concentrations, suggesting that public transit may be a point source of human exposure to titanium. The median titanium air concentrations outside of private cars (7.3 x 10^{-6} to 1.6 x 10^{-5} mg/m^3) were higher than inside private cars (6.1 x 10^{-6} to 1.0 x 10^{-5} mg/m^3), but lower than highest median air concentration reported on subways (Health Canada 2020h). Intake of titanium from air on public transit was not factored into the daily intake estimates in this exposure assessment but was considered as a point source of inhalation exposure in risk characterization (Table 5-1). Titanium was also measured in $PM_{2.5}$ samples from indoor and outdoor air in schools in Ottawa, Ontario. The median titanium concentration in indoor air was 5.5 x 10^{-6} mg/m^3 (n=133) and the median titanium concentration in outdoor air was 2.2 x 10^{-5} mg/m^3 (n=125) (Health Canada 2020d). The concentration of titanium measured in air in schools was greater than average titanium concentrations measured in ambient air. Similar to public transit, intake of titanium from air in schools was not factored into the daily intake estimates in this exposure assessment but was considered as a point source of inhalation exposure in risk characterization (Table 5-4**Error! Reference source not found.**).

To compare exposure between age groups, estimates of daily titanium intake from environmental media, food and drinking water were derived and presented in Appendix A, Table A-5. Intake of titanium from environmental media, food and drinking water ranged from 1.4 x 10^{-2} mg/kg bw/day for formula-fed infants 0 to 5 months old to 4.1 mg/kg bw/day for children 4 to 8 and 9 to 13 years old. Diet was the primary source of exposure for human milk-fed infants 0 to 5 months old and all age groups 6 months old and older. Dust was the primary source of exposure for formula-fed infants 0 to 5 months old, followed by diet. Estimated dietary intake of titanium from country foods in Northern Saskatchewan will not be brought forward to risk characterization as the highest estimated intake of 2.4 x 10^{-3} mg Ti/kg bw/day for 1 year old children in Stony

Rapids is lower than the highest mean daily intake of 4.1 mg/kg bw/day for children between 4 and 13 years old in the general Canadian population.

Table 5-1. Summary of titanium air concentration data (mg/m^3)

Exposure scenario	Ti daily air concentrations (mg/m^3)
Environmental media, $PM_{2.5}$ daily air concentration[a]	1.6×10^{-6}
Environmental media, daily air concentration point source influence[b]	1.0×10^{-3}
Environmental media, $PM_{2.5}$ daily air concentration, transit influence[c]	3.3×10^{-6}
Environmental media, $PM_{2.5}$ daily air concentration, school influence[d]	2.7×10^{-6}

Abbreviations: mg/m^3, milligram per cubic meter; $PM_{2.5}$, particulate matter with aerodynamic diameter of 2.5 µm or less; Ti, titanium

[a] Daily air concentration estimated using median 24-hour outdoor air sample $PM_{2.5}$ of 2.6×10^{-6} mg/m^3 (n=447) measured in Windsor, Ontario (Rasmussen 2017) and median 24-hour indoor air sample $PM_{2.5}$ of 1.4×10^{-6} mg/m^3 (n=437) measured in Windsor, Ontario (Rasmussen 2017). Canadians are assumed to spend 3 hours outdoors and 21 hours indoors each day (Health Canada 1998). Daily air concentration = (concentration Ti outdoor air x (3 hours/ 24 hours)) + (concentration Ti indoor air x (21 hours/ 24 hours)).

[b] Daily air concentration, point source influence estimated using ambient air concentration reported in industrialized areas in the US of 1.0×10^{-3} mg/m^3 (IPCS 1982; Jin and Berlin 2015; Woodruff et al. 2017). In the absence of data on titanium concentration in indoor air in the vicinity of a point source of release the titanium air concentration is assumed to be constant over a 24-hour period each day.

[c] Daily air concentration, transit influence estimated using median 24-hour $PM_{2.5}$ personal air sample from subway of 1.8×10^{-5} mg/m^3 and median 24-hour outdoor air sample $PM_{2.5}$ of 2.6×10^{-6} mg/m^3 (n=447) measured in Windsor, Ontario (Rasmussen 2017). The largest median $PM_{2.5}$ titanium concentration reported in data sets from Ottawa, Toronto, Montreal and Vancouver was assumed to represent median titanium air concentration as a conservative assumption. For time not spent on transit the titanium concentration in outdoor air is used as a conservative assumption as it is higher than the titanium concentration in indoor air. Individuals are assumed to spend 70 minutes on transit per day (van Ryswyk et al. 2017). Daily air concentration, transit influence = (concentration Ti personal air, subway x (70 minutes / 1440 minutes)) + (concentration Ti outdoor air x (1370 minutes/1440 minutes)).

[d] Daily air concentration, school influence estimated using median 24-hour outdoor air sample $PM_{2.5}$ of 2.6×10^{-6} mg $/m^3$ (n=447) measured in Windsor, Ontario (Rasmussen 2017), median 24-hour indoor air sample $PM_{2.5}$ of 1.4×10^{-6} mg/m^3 (n=437) measured in Windsor, Ontario (Rasmussen 2017) and median 8-hour personal indoor air sample $PM_{2.5}$ of 5.5×10^{-6} mg/m^3 (n=133) measured in the 2013 Ottawa School Study (Health Canada 2020d). School aged Canadians are assumed to spend 3 hours outdoors, 14.5 hours indoors each day and 6.5 hours indoors at school (Health Canada 1998; MacNeill et al. 2016). Daily air concentration, school influence = (concentration Ti outdoor air x (3 hours/ 24 hours)) + (concentration Ti indoor air x (14.5 hours/ 24 hours)) + (concentration Ti indoor school air x (6.5 hours/ 24 hours)).

5.2.2 Products available to consumers

The 13 titanium-containing substances have widespread industrial, commercial and consumer uses that may contribute to daily exposure. As outlined in the sources and uses section, substances in the Titanium-containing Substances Group are present in a wide range of products available to consumers. Exposures to titanium from products available to consumers, where use may contribute to systemic levels of titanium, are captured in the biomonitoring data. Inhalation exposure may result in portal-of-entry

effects in the lungs. Therefore, exposure was estimated for products available to consumers which could lead to potential inhalation exposure to titanium (Table 5-2).

Inhalation exposure assessment of the Titanium-containing Substances Group

In Canada, titanium tetraisopropanolate, titanium tetrakis(2-ethylhexanolate), rutile (TiO_2), dititanium trioxide (Ti_2O_3) and titanium dioxide (TiO_2) (CAS RNs 549-69-9, 1070-10-6, 1317-80-2, 1344-54-3 and 13463-67-7, respectively) were found in a range of aerosol or spray products and loose powder products where use may result in inhalation exposure. These products include self-care products (that is, cosmetics, natural health products and non-prescription drugs), disinfectant surface spray, powdered dish detergent, aerosol water repellant spray, aerosol boot protector spray, aerosol adhesives and sealants, spray automotive products, paints and coatings, cement, spray ceiling and wall texture, tile grout and floor coatings (personal communication, emails from the CHPSD, Health Canada, to the ESRAB, Health Canada, dated between March 29, 2018 and December 8, 2020; unreferenced; personal communication, emails from the NNHPD, Health Canada, to the ESRAB, Health Canada, dated March 9, 2018; unreferenced; personal communication, email from the TPD, Health Canada, to the ESRAB, Health Canada, dated March 6, 2018; unreferenced; Health Canada 2019; CPID [modified 2022]; CPISI [modified 2022]). The other eight substances in the Titanium-containing Substances Group were not found in products available to consumers that may result in inhalation exposure. All concentrations of titanium-containing substances in products available to consumers were converted to titanium equivalents based on composition and molecular weight. Exposure estimates for products resulting in the highest air concentrations of titanium from each product category are included in this exposure assessment.

Air concentrations of titanium from the use of aerosol and trigger or pump spray products were modeled using the Consumer Exposure Web Model v.1.0.7 (ConsExpo Web 2020), a computational modeling program intended to estimate exposure of the general population to products available to consumers. Refinements to certain default model parameters for aerosol and/or spray product scenarios were made in order to generate the most relevant exposure estimates for each sentinel self-care product type. Air concentrations were estimated for the use of self-care products formulated as aerosols and trigger or pump sprays including aerosol sunscreen spray, aerosol body make-up, aerosol hair styling spray, and aerosol temporary hair colour. Concentrations of titanium in aerosol and trigger or pump spray self-care products ranged from 0.06% to 18% (personal communication, emails from the CHPSD, Health Canada, to the ESRAB, Health Canada, dated between March 29, 2018 and December 08, 2020; unreferenced; email from the TPD, Health Canada, to the ESRAB, Health Canada, dated March 06, 2018; unreferenced). Air concentrations of titanium from the use of aerosol and trigger or pump spray products were amortized over 24 hours to generate mean daily air concentrations. The highest estimated amortized daily air concentration from aerosol and trigger or pump spray self-care products was 2.8×10^{-3} mg Ti/m^3 from the use of aerosol leg foundation spray. This scenario is presented as the sentinel

exposure scenario, covering exposure from other aerosol and trigger or pump spray self-care products.

In addition to self-care product uses, scenarios were modelled to estimate exposure from the use of a spray disinfectant product, and use of an aerosol spray paint can (personal communication, email from the TPD, Health Canada, to the ESRAB, Health Canada, dated March 06, 2018; unreferenced; Health Canada 2019; CPID [modified 2022]). Mean daily air concentrations were derived by amortizing exposure over 24 hours and considering the frequency of use of spray disinfectant product and aerosol spray paint can. Estimated mean daily air concentration from the use of a spray disinfectant was 2.5×10^{-3} mg Ti/m^3 while the mean daily air concentration from the use of an aerosol spray paint can was 4.5×10^{-3} mg Ti/m^3.

Air concentrations were also estimated for self-care products formulated as loose powders with the potential for inhalation of respirable titanium-containing particles. These products include body powder, powdered face makeup, and powdered face make up with SPF. Concentrations of titanium in powdered self-care products ranged from 0.06% to 60% (personal communication, emails from the CHPSD, Health Canada, to the ESRAB, Health Canada, dated between March 29, 2018 and December 8, 2020; unreferenced; personal communication, email from the NNHPD, Health Canada, to the ESRAB, Health Canada, dated March 9, 2018; unreferenced). Products formulated as pressed powders were not identified as a potential source of exposure of concern because these formulations contain coarser particles and binders, such as oils or waxes, which help bind the particles together and do not lead to the formation of a “dust cloud” available for inhalation during the use of these products.

Air concentrations of powdered self-care products were estimated using experimentally measured average PM air concentration data of poorly soluble particles from the use of loose powdered cosmetics. Several studies of air concentrations generated from the use of powdered self-care products were considered (Nazarenko et al. 2012; Anderson et al. 2017; Rasmussen et al. 2019; Oh et al. 2021). Nazarenko et al. (2012) measured the air concentration of PM from the simulated use of cosmetic powders in particle number concentrations. Oh et al. (2021) measured air concentrations generated from the simulated use of eyebrow powders in mass concentration. Data from Nazarenko et al. (2012) were not used to estimate air concentrations of titanium dioxide from the use of powdered self-care products in this assessment as the mass per volume air concentration data were not reported (only number of particles per volume of air). Data from Oh et al. (2021) were not used to estimate air concentrations of titanium dioxide from the use of powdered self-care products in this exposure assessment as the product type (eyebrow powder) could lead to underestimation of air concentrations from body powders and face powders where a larger amount of product may be used, over a greater body surface application area.

Of the available data, Anderson et al. (2017) and Rasmussen et al. (2019) provide the best and most relevant available data to model the product scenarios included in

this exposure assessment as the data in these studies are reported in mass concentration and the products analyzed are representative of the product types considered within this exposure assessment. In studies by Anderson et al. (2017) and Rasmussen et al. (2019), average PM of aerodynamic diameter of 4 µm or less (PM_4) air concentrations of talc, a poorly soluble mineral common in cosmetics, were estimated from the use of loose body and face powdered products. Average air concentrations from Anderson et al. (2017) were combined with the body and face replicates from Rasmussen et al. (2019) to obtain an overall average PM_4 event air concentration of 1.36 ± 0.97 mg/m^3 (ECCC, HC 2021). This air concentration was used to estimate air concentrations of titanium from the use of self-care products considering the concentration of titanium present in the products. Use of talc PM_4 data as a surrogate for titanium is based on their physical similarities as poorly soluble particles and use in similar types of products available to consumers. The highest estimated mean daily air concentration from loose powder self-care products was 2.8 x 10^{-3} mg Ti/m^3 from the use of loose powder face makeup. This scenario is presented as the sentinel exposure scenario, covering exposure from other loose powder self-care products.

Additionally, scenarios were modeled to represent pouring of solid powder prior to mixing, representing potential inhalation exposure from mixing of a powdered bath product into a bath, pouring powdered dish detergent and mixing of tile grout. Air concentrations of titanium generated from pouring powdered products, were estimated based on unit exposure data from the Pesticide Handlers Exposure Database (PHED). Eight-hour time weighted average (TWA) air concentration estimates were generated using the PHED 8-hour time weight average unit exposure for open pour powder exposure to antimicrobial products (7.8 x 10^{-3} mg/m^3/lb ai) (US EPA 2016). Mean daily air concentrations were derived by amortizing exposure over 24 hours based on duration of exposure and frequency of use. Mean daily air concentrations from pouring powdered products available to consumers ranged from 2.6 x 10^{-6} to 1.9 x 10^{-5} mg Ti/m^3.

The exposure scenarios for aerosol, spray and loose powdered products that resulted in the highest air concentrations are presented in Table 5-2. Adjusted 4-hour air concentrations were derived for products with infrequent or intermittent use patterns. On the basis of the duration and nature of effects seen in the toxicity data used to characterize risk, the mean event air concentrations of titanium from the use of products were amortized over 24 hours based on duration of exposure and frequency of use to represent continuous exposure. Details of all exposure scenarios and input values for the models are provided in Appendix B, Table B-1 including the refinements to defaults.

Table 5-2. Estimated titanium dioxide air concentrations from the use of products available to consumers

Product category	Exposure scenario	Age group[a]	Mean event air concentration (mg Ti/m^3)	Adjusted 4-hour air concentration (mg Ti/m^3)[b]	Mean daily air concentration (mg Ti/m^3)
Self-care, cosmetic	Using leg foundation (spray)	Adult	0.8	NA	2.8×10^{-3}
Self-care, cosmetic	Using face make-up (loose powder)	Adult	0.82	NA	2.8×10^{-3}
Self-care, cosmetic	Pouring powdered bath product	Adult	2.0×10^{-4} [c]	NA	1.9×10^{-5}
Self-care, cosmetic	Using hair colour temporary (spray)	Adult	0.9	1.9×10^{-2}	5.9×10^{-5}
Cleaning product, (NPD–NMI)	Using surface disinfectant spray	Adult	3.6×10^{-2}	NA	1.5×10^{-3}
Cleaning product	Pouring powdered dish detergent	Adult	7.9×10^{-6} [c]	NA	2.6×10^{-6}
Paints and coatings	Aerosol spray can	Adult	59	4.9	4.5×10^{-3}
DIY product	Pouring powdered tile grout	Adult	2.5×10^{-2} [c]	5.2×10^{-2}	1.2×10^{-5}

Abbreviations: DIY, do it yourself; NA, not applicable; NMI, non-medicinal ingredient; NPD, non-prescription drug; mg/m^3, milligram per cubic meter; Ti, titanium.

[a] Age group(s) identified are those with the highest estimated daily exposure based on the event air concentration and frequency of use.

[b] Air concentrations adjusted to 4-hour average air concentrations to match the duration of exposure in the acute hazard study. Adjusted 4-hour air concentration (mg/m^3) = Mean event air concentration (mg/m^3) x (Exposure duration (hour) / 4 hours).

[c] The reported mean event air concentration is an 8-hour time-weighted average (TWA) air concentration based on the availability of unit exposure values.

Additional use scenarios with the potential for inhalation exposure to titanium dioxide were considered, including aerosol fragrance, pump body spray, aerosol body moisturizer, aerosol sunscreen, aerosol sunless tanning products, aerosol hair spray, aerosol dry shampoo, aerosol face make-up, aerosol face moisturizer, aerosol nail

polish, powdered deodorant, powdered body moisturizer, powdered body makeup, other loose powdered makeup products (for example, blush, eyeshadow), powdered face cleanser, pneumatic paint sprayer, aerosol adhesives and sealants, spray ceiling and wall texture and spray floor coatings but resulted in lower mean daily air concentrations than those presented in Table 5-2. Adjusted 4-hour exposures from products with infrequent or intermittent use patterns were calculated but were not brought forward to risk characterization as there were no effects observed in acute toxicity studies. Estimated exposures from the products with infrequent or intermittent use patterns were adjusted to continuous exposure scenarios and considered in risk characterization as the sentinel exposure scenarios when applicable.

5.2.3 Biomonitoring data

Total titanium concentration in whole blood was used to estimate exposure of the general population to the Titanium-containing Substances Group. The human health risks of the 13 titanium-containing substances were characterized using the Biomonitoring-based Approach 2 (Health Canada 2016a). The Biomonitoring-based Approach 2 compares human biomonitoring data (as a measure of exposure) against biomonitoring guidance values that are consistent with available health-based exposure guidance values, such as BEs, to assess if substances are of low concern for human health. Total concentrations of titanium in whole blood provide a biologically relevant, integrated measure of systemic exposures that may occur across multiple routes (for example, oral, dermal and inhalation) and from various sources, including environmental media, food, and frequent or daily use of products available to consumers. There are very limited substance-specific exposure data, thus data on the total metal moiety was considered to be an acceptable, conservative surrogate as total metal moiety biomonitoring data include exposures from all bioavailable forms of the element. Therefore, exposure characterization of systemic effects through this moiety-based approach may be applicable to titanium-containing substances beyond the substances included in the Titanium-containing Substances Group. The Titanium-containing Substances Group did not meet the criteria to be assessed using Biomonitoring-based Approach 1 (Health Canada 2016b) as the limit of detection in available biomonitoring data was not sufficiently low (Jayawardene et al. 2021). Sufficient high-quality biomonitoring data exist for titanium to adequately characterize exposure to the Canadian population, including specific sub-populations of interest who may have the potential for elevated exposure, such as children, pregnant people and certain Indigenous populations.

Canadian population level whole blood titanium concentrations were generated in a biobank project (Jayawardene et al. 2021). In this project, whole blood samples, collected and preserved from the Canadian Health Measures Survey (CHMS) Cycle 2 (5 752 samples), were analysed by inductively coupled plasma-mass spectrometry at the Health Canada's Health Products Laboratory in Longueuil, Quebec, for their titanium concentrations (Health Canada 2013; Jayawardene et al. 2021). The CHMS is a national survey carried out by Statistics Canada in partnership with Health Canada and

Public Health Agency of Canada, which collects information from Canadians about their general health (Health Canada 2013). It is designed to be nationally representative[9], and includes a biomonitoring component. The CHMS is not a targeted survey, and thus does not target individuals with known high metal exposure nor those living near point sources of exposure. The CHMS Cycle 2 samples were collected from 2009 to 2011 in Canadians aged 3 to 79, including pregnant women and both fasting and non-fasting individuals, at 18 sites across Canada (Health Canada 2013). Titanium was not detected in 99.97% of the Canadian population (ages 3 to 79), at or above the limit of detection of 10 µg/L (Table 5-3) (Jayawardene et al. 2021). The median and 95th percentile titanium concentrations were below the limit of detection.

Table 5-3. **Whole blood titanium concentrations (µg/L) measured in biobank samples from the CHMS – Cycle 2**

Substance	Number of samples	LOD (µg/L)	Median (µg/L)	95th percentile (µg/L)	Detection frequency[a]
Titanium	5752	10	<10	<10	0.03

Abbreviation: CHMS, Canadian Health Measures Survey; LOD, limit of detection; µg/L, microgram per litre
[a] Percent of population with concentrations at or above the limit of detection (10 µg/L).

In addition to population level CHMS biomonitoring data, Canadian data from pregnant women in Northern Saskatchewan and control or pre-operative data from studies that measured titanium concentrations in blood of people with metallic orthopedic implants were considered. The studies were carefully selected for inclusion in this risk assessment as analysis of titanium in complex matrices is susceptible to analytical challenges, such as spectral interferences in conventional analytical methods used for trace element determination and potential inadvertent contamination of samples (Rodushkin and Ödman 2001; Sampson and Hart 2012; Balcaen et al. 2014; Barry et al. 2020). A wide range of baseline whole blood and/or serum titanium concentrations have been reported in literature over the past years. Some of the variation in baseline whole blood or serum titanium concentrations may be due to insufficient sensitivity and/or selectivity of conventional analytical methods used for trace element determination to

[9] The Canadian Health Measures Survey cycle 2 covers the population 3 to 79 years of age living in the ten provinces and the three territories. Excluded from the survey's coverage are: persons living on reserves and other Indigenous settlements in the provinces; full-time members of the Canadian Forces; the institutionalized population and residents of certain remote regions. Altogether these exclusions represent less than 4% of the target population.

accurately quantify the trace levels of titanium in complex matrices such as whole blood and serum (Barry et al. 2020).

Titanium was included in the Northern Saskatchewan Prenatal Biomonitoring Study (Saskatchewan Ministry of Health 2019). In this study, a series of environmental chemicals and metals were monitored in the blood serum of pregnant women (n=841) residing in Northern Saskatchewan between 2011 and 2013 (Saskatchewan Ministry of Health 2019). The study was conducted in Northern Saskatchewan with a population of approximately 40,000 people across 70 communities. Close to 87% of the population residing in the area self-identify as Indigenous persons (Saskatchewan Ministry of Health 2019). Blood samples were pooled into six pools by geographical area. The median concentration of titanium measured in each of the geographic pooled samples was below the limit of detection of 5 µg/L.

Most available studies reporting titanium concentrations in blood are focused on the use of titanium biomonitoring data to assess the condition and degradation of metallic orthopedic implants (Sampson and Hart 2012; Balcaen et al. 2014; Barry et al. 2020). Recent studies of patients with metallic orthotic implants using highly sensitive and selective analytical methods have reported mean concentrations of titanium in whole blood and serum pre-operatively or in control groups between 0.2 and 2.5 µg/L (Dunstan et al. 2005; Richardson et al. 2008; Sarmiento-González et al. 2008; Engh et al. 2009; Vendittoli et al. 2010, 2011, 2013; Nuevo-Ordóñez et al. 2011; Barry et al. 2013, 2020; Omlor et al. 2013; Balcaen et al. 2014; Cundy et al. 2014; Gofton et al. 2015; Nam et al. 2015, 2019; Barlow et al. 2017; Koller et al. 2018; Temiz et al. 2018; Reiner et al. 2019). Furthermore, recent studies of titanium in blood using high resolution analytical methods consistently reported baseline levels of titanium lower than 1 µg/L (Swiatkowska et al. 2019).

Whole blood titanium concentrations from the CHMS will be used to characterize systemic exposure to Canadians. This biomonitoring data is considered to be an integrated measure of systemic titanium from all routes and sources including exposure from environmental media, food, drinking water and frequent or daily use products. The CHMS biomonitoring dataset includes Canadians aged 3 to 79 years and is considered to be protective of younger age groups not covered by the survey (under 3 years of age) as children aged 4 to 13 had the highest intake from environmental media, food and drinking water. Titanium blood concentrations indicate that population-level exposure is below the limit of detection of 10 µg/L. This is considered to be a conservative estimate when compared with titanium blood concentrations measured from pregnant women and Indigenous women in Northern Saskatchewan (< 5 µg/L) and data from control and pre-operative individuals in studies of metallic orthotic implants (0.2 to 2.5 µg/L).

5.2.4 Consideration of subpopulations who may have greater exposure

There are groups of individuals within the Canadian population who, due to greater exposure, may be more vulnerable to experiencing adverse health effects from

exposure to substances. Certain subpopulations have the potential for increased exposure due to differences in physical characteristics (for example, body weight, breathing rate), lifestage (for example, infancy, pregnancy), behaviours (for example, mouthing and ingestion of non-food items, crawling), cultural influences (for example, unique diets or product use), socio-economic factors (for example, substandard housing, limited consumer choice) or geographical differences (for example, living in the vicinity of commercial or industrial facilities). The potential for elevated exposure to titanium within the Canadian population was examined. Exposure estimates are routinely assessed by age to take into consideration physical and behavioural differences during different stages of life. When data is available, additional exposure factors are taken into consideration.

In this exposure assessment, exposure estimates from environmental media, food, drinking water, human milk, infant formula and from products were derived for different age groups to take into account differences in physiology, life stage and behaviours. Children aged 4 to 13 had higher intakes from environmental media, food and drinking water than adults. Intake of titanium from the consumption of country foods by Indigenous populations in Northern Saskatchewan was lower than the estimated mean dietary intake of titanium for the general population. Biomonitoring data were available for the Canadian population from the CHMS and from pregnant women and Indigenous women living in Northern Saskatchewan. An analysis of the potential for elevated exposure within the Canadian population could not be conducted as concentrations of titanium in the CHMS biomonitoring data were consistently below the limit of detection. However, the biomonitoring data brought forward to risk characterization was protective of exposures measured in pregnant women and Indigenous women from Northern Saskatchewan. In addition, measured and modelled data were available to characterize airborne titanium exposure among children in school, transit users and people living in the vicinity of industrial point sources. Airborne titanium concentrations were higher near industrial point sources compared to ambient air. All of these considerations were taken in account when characterizing exposure and risk to Canadians.

5.3 Risk characterization

The potential for cumulative effects was considered in this assessment by examining cumulative exposures from the broader moiety of titanium. Due to the availability of adequate and representative Canadian biomonitoring data and a biomonitoring guidance value for titanium (that is, a BE), characterization of the potential for harm to human health from systemic exposure to the Titanium-containing Substances Group was based on the Biomonitoring-based Approach 2 as noted in section 5.2.3 (Health Canada 2016a).

Systemic exposure to total titanium in the Canadian population was characterized using biomonitoring data from the CHMS (Cycle 2). This data is representative of exposures that may occur across multiple routes and from various sources, including environmental media, food, and frequent or daily use of products available to

consumers. The 95th percentile whole blood titanium concentration data was below the detection limit of 10 µg/L (Table 5-3) and was not detected in 99.97% of the Canadian population (Jayawardene et al. 2021). Available biomonitoring data, estimated intakes from environmental media and diet and estimated intake from country foods, indicate that the CHMS data is considered to be protective of titanium measured in Indigenous populations and pregnant women in Canada as well as infants and children. Although there are no biomonitoring data from the CHMS Cycle 2 biobank for children under 3 years of age, exposure for this age group from environmental media, food and drinking water is lower than children aged 4 to 13 who are captured in the CHMS dataset.

A multi-compartmental pharmacokinetic model published by Ramoju et al. (2020) was used to derive a whole blood BE of 65 µg/L for the NOAEL of 623 mg Ti/kg bw/day (Ramoju et al. 2020) with an UF of 25 (2.5x inter-species toxicodynamics and 10x for intra-species variation). Exposure to total titanium in the Canadian population, characterized by the detection limit of titanium in whole blood of 10 µg/L, was below the derived BE of 65 µg/L and considered to be low enough to account for uncertainties in the health effects and exposure data used to characterize risk. This indicates that the 13 titanium-containing substances are of low concern to the health of the general population of Canada at current levels of systemic exposure.

For inhalation exposure, inhalation toxicity data for titanium dioxide was used as surrogate data for the risk characterization of inhalation exposure of the 13 titanium substances in the group.

The LOAEC of 10 mg TiO_2/m^3 (6.0 Ti/m^3) based on treatment-related lung effects (portal-of-entry effects) in rats from Lee et al. (1985) was selected as the critical POD for risk characterization of chronic inhalation exposure to titanium in the general population. The LOAEC (that is, 10 mg TiO_2/m^3) was converted to continuous titanium exposure concentration of 1.1 mg Ti/m^3 as detailed in section 5.1.4. The conversion of the critical POD based on titanium dioxide to titanium concentration was done to support the use of the POD for all titanium-containing substances in the group. The adjustment for continuous exposure was conducted to address the differences in exposure duration between the tested animals in the critical health effects study and the duration of exposure from the use of products available to consumers. Episodic exposures from product use are expected to increase lung load over time due to slow lung clearance of titanium particles. Quantification of risk to acute inhalation exposures to titanium was not conducted as there were no adverse effects observed up to the limit dose of 5090 mg TiO_2/m^3 (3 051 mg Ti/m^3) tested in an acute inhalation study (REACH [modified 2022]).

Measurements of titanium in PM in air, including indoor, outdoor and ambient air in proximity to point sources of exposure were used to characterize inhalation exposure to titanium-containing substances. A comparison of the LOAEC of 1.1 mg Ti /m^3 for portal-of-entry effects to the air concentrations of titanium in outdoor, personal and ambient air in proximity to point sources resulted in route specific margins of exposure (MOEs) in

the range of 1 100 to 733 333 (Table 5-4). In addition, there is potential for inhalation exposure to titanium-containing substances from the use of spray products (aerosol, pump) and loose powder products available to consumers. Exposure estimates were derived for sentinel exposure scenarios to characterize risk to the general population. A comparison of the LOAEC of 1.1 mg Ti/m^3 for portal-of-entry effects and the estimated air concentrations of titanium from the use of spray and loose powder products available to consumers resulted in MOEs ranging from 245 to 687 500 (Table 5-5).

The derived MOEs for inhalation exposure are considered adequate to protect the general population from route-specific adverse effects of inhalation exposure to titanium from products. The MOE for paints and coatings applied via an aerosol spray can was slightly below the target MOE; however, it is acknowledged that the ConsExpo model used to generate this exposure estimate provides some degree of conservatism. In addition, the POD is based on respiratory tract effects that would be expected to be reversible within the long period between intermittent exposures with this use pattern. On the basis of the conservative parameters used in modelling of exposures and the critical endpoint from a chronic inhalation study, the calculated MOEs are considered adequate to account for uncertainties in the inhalation health effects and exposure data used to characterize risk.

Table 5-4. Inhalation exposure estimates for titanium and resulting MOEs

Exposure scenario	Daily Ti air concentrations (mg/m^3)	MOE[a,b]
Environmental media, $PM_{2.5}$ daily air concentration	1.5×10^{-6}	733 333
Environmental media, daily air concentration point source influence	1.0×10^{-3}	1 100
Environmental media, $PM_{2.5}$ daily air concentration, transit influence	3.3×10^{-6}	333 333
Environmental media, $PM_{2.5}$ daily air concentration, school influence	2.7×10^{-6}	407 407

Abbreviations: mg/m^3, milligram per cubic meter; MOE, margin of exposure; $PM_{2.5}$, particulate matter with aerodynamic diameter of 2.5 µm or less; Ti, titanium

[a] MOEs calculated based on the POD of 1.1 mg Ti/m^3 for portal-of-entry effects from the LOAEC of 6 Ti/m^3 adjusted for continuous exposure from Lee et al. (1985).

[b] Target MOE = 300 (10x inter-species variation; 10x intra-species variation; 3x for LOAEC extrapolated to NOAEC).

Table 5-5. Inhalation exposure estimates for titanium and resulting MOEs

Product category; Exposure scenario	Mean daily air concentrations (mg Ti/m^3)[a]	MOE[b, c]
Self-care; Applying leg foundation (cosmetic), Adult	2.8×10^{-3}	393
Self-care; Using face make-up (loose powder) (cosmetic), Adult	2.8×10^{-3}	393

Product category; Exposure scenario	Mean daily air concentrations (mg Ti/m^3)[a]	MOE[b, c]
Self-care; Pouring powdered bath product (cosmetic), Adult	1.9 x 10^{-5}	57 895
Cleaning product; Using disinfectant (spray) (NPD – NMI), Adult	1.5 x 10^{-3}	733
Cleaning products; Pouring powdered dish detergent, Adult	1.6 x 10^{-6}	687 500
Paints and coatings; Aerosol spray paint can, Adult	4.5 x 10^{-3}	245[d]

Abbreviations: DIY, do it yourself; mg/m^3, milligram per cubic meter; MOE, margin of exposure; NMI, non-medicinal ingredient; NPD, non-prescription drug; Ti, titanium.
[a] Estimated titanium exposure air concentrations were amortized over 24 hours, based on duration of exposure and frequency of use, to represent average daily air concentration.
[b] MOEs calculated based on the POD of 1.1 mg Ti/m^3 for portal-of-entry effects from the LOAEC of 6 Ti/m^3 adjusted for continuous exposure from Lee et al. (1985).
[c] Target MOE = 300 (10x inter-species variation; 10x intra-species variation; 3x for LOAEC to NOAEC).
[d] Considered adequate due to conservativisms in the ConsExpo model parameters used to generate the exposure estimate, as well as the reversibility of effects that would be expected between intermittent exposures.

5.4 Uncertainties in the evaluation of risk to human health

There is some uncertainty with the use of toxicokinetic and toxicity data from titanium dioxide as surrogate data for all titanium-containing substances in the group.

Some uncertainties with Biomonitoring-based Approach 2 (Health Canada 2016a) may include limited pharmacokinetic data in the derivation of a biomonitoring guidance value, and the variability in the quality and robustness of data available for the derivation of a biomonitoring guidance value (for example, BE) for titanium. It is also difficult to identify sources of exposure by using biomonitoring data alone; and therefore, this human health assessment considers information on sources and uses.

The pharmacokinetic model used for BE derivation assumed that the kinetic properties of intravenous exposure are applicable to simulate oral exposure scenarios. Although there is some uncertainty associated with this assumption, this approach is consistent with the evidence provided by various animal and human oral studies available for titanium dioxide microparticles.

The relevance of the biomarker to the dose metrics of titanium is considered to be low to medium. There is uncertainty due to low and variable oral bioavailability confounded by background levels (EFSA 2016) and the lack of any significant data relating the degree of toxicity to blood titanium.

While health effects of nanoscale particles have been reported for both oral and inhalation exposure, the toxicity associated with nanoscale particles is not explicitly considered in this human health assessment. Some titanium-containing substances,

such as food-grade titanium dioxide contain both nanoscale and microscale particles. The particle size distribution of food-grade titanium dioxide (including the percentage of nanoparticles that may be present) may vary and therefore, there is some uncertainty as to the particle size range in food-grade titanium dioxide that Canadians are exposed to as well as how closely the titanium dioxide test materials used in research studies resemble the forms of food-grade titanium dioxide that may be found in food in Canada. Additionally, it is unclear whether the composition of other substances in the Titanium-containing Substances Group also contain a fraction of nanoscale particles. The Government of Canada has committed to further addressing nanoscale forms of substances on the DSL including nanoscale titanium dioxide (ECCC, HC 2022; Health Canada [modified 2022a]).

6. Conclusion

Considering all available evidence presented in this draft assessment, there is low risk of harm to the environment from the 13 substances in the Titanium-containing Substances Group. It is proposed to conclude that the 13 substances in the Titanium-containing Substances Group do not meet the criteria under paragraphs 64(*a*) or (*b*) of CEPA as they are 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.

Considering all available lines of evidence presented in this draft assessment, it is proposed to conclude that the 13 substances in the Titanium-containing Substances Group do not meet the criteria under paragraph 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 in Canada to human life or health.

It is therefore proposed to conclude that the 13 substances in the Titanium-containing Substances Group do not meet any of the criteria set out in section 64 of CEPA.

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Appendix A. Exposure to environmental media, food and drinking water

Table A-1. General human exposure factors for different age groups used in scenarios[a]

Age groups	Body weight (kg)	Inhalation rate (m^3/day)	Soil ingestion rate (µg/day)	Dust ingestion rate (µg/day)
0 to 5 months	6.3	3.7	N/A	21.6
6 to 11 months	9.1	5.4	7.3	27.0
1 year	11	8.0	8.8	35.0
2 to 3 years	15	9.2	6.2	21.4
4 to 8 years	23	11.1	8.7	24.4
9 to 13 years	42	13.9	6.9	23.8
14 to 18 years	62	15.9	1.4	2.1
Adults (19+)	74	15.1	1.6	2.6

[a] Health Canada 2021b.

Table A-2. Concentrations of titanium in environmental media and food in Canada

Media	Median	95th percentile	n	Reference
NAPS outdoor air $PM_{2.5}$	0.874 ng/m^3	3.032 ng/m^3	969	NAPS 2015
NAPS outdoor air $PM_{2.5}$	1.28 ng/m^3	3.85 ng/m^3	820	NAPS 2016
NAPS outdoor air $PM_{2.5}$	1.65 ng/m^3	6.03 ng/m^3	1333	NAPS 2017
NAPS outdoor air $PM_{2.5}$	1.53 ng/m^3	5.66 ng/m^3	1190	NAPS 2018
Outdoor air $PM_{2.5}$	2.57 ng/m^3	7.01 ng/m^3	447	Rasmussen 2017
Outdoor air $PM_{2.5}$	1.04 ng/m^3	6.51 ng/m^3	610	Health Canada 2020b
Outdoor air $PM_{2.5}$	2.37 ng/m^3	6.57 ng/m^3	512	Health Canada 2020c
Outdoor air $PM_{2.5}$	2.16 ng/m^3	9.47 ng/m^3	125	Health Canada 2020d
Outdoor air $PM_{2.5}$	3.46 ng/m^3	8.89 ng/m^3	105	Health Canada 2020e
Outdoor air $PM_{2.5}$	0.727 ng/m^3	3.19 ng/m^3	55	Health Canada 2020f
Outdoor air $PM_{2.5}$	0.421 ng/m^3	6.63 ng/m^3	131	Health Canada 2020g
Outdoor air $PM_{2.5}$	0.78 to 2.0 ng/m^3	1.5 to 67 ng/m^3	230	WBEA 2019
Outdoor air $PM_{2.5}$	0.81 to 2.2 ng/m^3	6.3 to 10 ng/m^3	302	WBEA 2020
Indoor air $PM_{2.5}$	1.42 ng/m^3	5.22 ng/m^3	437	Rasmussen 2017

Media	Median	95th percentile	n	Reference
Personal air $PM_{2.5}$	1.74 ng/m^3	9.5 ng/m^3	445	Rasmussen 2017
Indoor air $PM_{2.5}$	0.723 ng/m^3	4.83 ng/m^3	595	Health Canada 2020b
Indoor air $PM_{2.5}$	5.53 ng/m^3	15.97 ng/m^3	133	Health Canada 2020d
Indoor air $PM_{2.5}$	2.50 ng/m^3	12.38 ng/m^3	79	Health Canada 2020g
Personal air $PM_{2.5}$, bus	6.00 to 7.95 ng/m^3	12.91 to 60.74 ng/m^3	54	Health Canada 2020h
Personal air $PM_{2.5}$, subway	4.49 to 17.63 ng/m^3	9.25 to 67.25 ng/m^3	54	Health Canada 2020h
Indoor air $PM_{2.5}$, private car	6.07 to 10.48 ng/m^3	11.78 to 14.54 ng/m^3	22	Health Canada 2020h
Outdoor air $PM_{2.5}$, private car	7.32 to 15.62 ng/m^3	26.27 to 101.12 ng/m^3	22	Health Canada 2020h
House dust	2100 µg/g	4005 µg/g	1025	Rasmussen 2017
Infant formula, dairy-based, powder	0.3 ppm (mean)	0.42 ppm (maximum)	52	CFIA 2020
Infant formula, soy-based, powder	0.32 ppm (mean)	0.54 ppm (maximum)	7	CFIA 2020
Drinking water, National survey in distribution systems	<5.0 µg/L	<5.0 µg/L	97	Tugulea 2016
Soil, Ontario	3 070 mg/kg	4 939 mg/kg	483	Ontario [modified 2015]

Abbreviations: n, number of observations/samples; $PM_{2.5}$, particulate matter of aerodynamic diameter of 2.5 µm or less; ppm, parts per million

Table A-3. Mean and 95th percentile titanium dioxide dietary exposure estimates for the refined non-brand-loyal consumer scenario (EFSA 2021)

Age group	Mean intake (mg TiO_2/ kg bw/day)	Mean intake (mg Ti/ kg bw/day)	95th percentile intake (mg TiO_2/ kg bw/day)	95th percentile intake (mg Ti/ kg bw/day)
12 weeks to 11 months	0.03 to 2.9	0.02 to 1.7	0.1 to 9.9	0.06 to 5.9
12 months to 35 months	0.6 to 6.0	0.36 to 3.6	1.9 to 27.5	1.1 to 16.5
3 years to 9 years old	0.9 to 6.9	0.54 to 4.1	2.5 to 23.7	1.5 to 14.2
10 years to 17 years	0.6 to 3.6	0.36 to 2.1	1.6 to 13.2	0.96 to 7.9
18 to 64 years old	0.3 to 3.8	0.18 to 2.3	1.2 to 9.5	0.72 to 5.7
>65 years old	0.2 to 2.8	0.12 to 1.7	0.9 to 7.1	0.54 to 4.3

Abbreviations: TiO_2, titanium dioxide

Table A-4. Dietary intake (mg/kg bw/day) of titanium by people consuming country foods in six communities in Eastern Athabasca basin (EARMP [modified 2021b])[a]

Age group (yr)	Black Lake	Fond du Lac	Stony Rapids	Wollaston Lake	Camsell Portage[b]	Uranium City[c]
Adult	3.4×10^{-4}	3.4×10^{-4}	3.6×10^{-4}	3.5×10^{-4}	3.5×10^{-5}	7.9×10^{-5}
14 to 18	3.3×10^{-4}	3.3×10^{-4}	4.5×10^{-4}	3.9×10^{-4}	5.9×10^{-5}	8.6×10^{-5}
9 to 13	4.9×10^{-4}	4.8×10^{-4}	6.6×10^{-4}	5.7×10^{-4}	8.8×10^{-5}	1.3×10^{-4}
4 to 8	7.8×10^{-4}	7.8×10^{-4}	1.1×10^{-3}	9.8×10^{-4}	1.3×10^{-4}	1.9×10^{-4}
2 to 3	1.2×10^{-3}	1.2×10^{-3}	1.8×10^{-3}	1.5×10^{-3}	1.4×10^{-3}	2.0×10^{-3}
1	1.7×10^{-3}	1.6×10^{-3}	2.4×10^{-3}	2.1×10^{-3}	1.8×10^{-4}	2.7×10^{-4}

Abbreviations: yr, years

[a] Dietary intake estimates were derived based methodology presented in EARMP 2017-2018 Human Health Risk Assessment (HHRA) (CanNorth 2018). Titanium occurrence data from 2015 to 2020 from the EARMP were combined and average values were calculated by calculating the mean for commodities with less than 10 samples and the 95% UCLM were derived for commodities with greater than or equal to 10 samples. Samples below the limit of detection were assumed to contain Ti content equal to the limit of detection. Consumption values from the EARMP 2017/2018 HHRA were used to derive intake estimates. Dietary intake =Σ (average concentration in commodity (mg/g) x daily consumption of commodity (g/day)/body weight (kg)).

[b] Dietary intake estimates do not include contribution from birds (grouse), or small mammals (snowshoe hare) as no concentrations of titanium were measured in samples collected in Camsell Portage from 2015 to 2020 as part of the EARMP.

[c] Dietary intake estimates do not include contribution from small mammals (snowshoe hare) as no concentrations of titanium were measured in samples collected in Uranium City from 2015 to 2020 as part of the EARMP.

Table A-5. Estimated average daily intake (mg/kg bw/day) of titanium by the general population in Canada by various age groups through environmental media, food and drinking water

Route of exposure	0 to 5 months[a] human milk fed[b]	0 to 5 months[a] formula fed[c]	6 to 11 months[d] human milk fed[b]	6 to 11 months[d] formula fed[c]	1 year	2 to 3 years	4 to 8 years	9 to 13 years	14 to 18 years	Greater than or equal to 19 years
Ambient air[d]	1.9×10^{-7}	1.9×10^{-7}	1.9×10^{-7}	1.9×10^{-7}	2.3×10^{-7}	2.0×10^{-7}	1.6×10^{-7}	1.06×10^{-7}	8.2×10^{-8}	6.6×10^{-8}
Indoor air[e]	7.3×10^{-7}	7.3×10^{-7}	7.4×10^{-7}	7.4×10^{-7}	9.0×10^{-7}	7.6×10^{-7}	6.0×10^{-7}	4.1×10^{-7}	3.2×10^{-7}	2.5×10^{-7}
Drinking water[f]	N/A	6.6×10^{-4}	N/A	4.2×10^{-4}	1.6×10^{-4}	1.4×10^{-4}	1.2×10^{-4}	8.8×10^{-5}	8.8×10^{-5}	1.0×10^{-4}
Food and beverages[g, h]	2.3×10^{-2}	6.3×10^{-3}	1.7	1.7	3.6	3.6	4.1	4.1	2.1	2.3
Soil[i]	N/A	N/A	2.5×10^{-3}	2.5×10^{-3}	2.5×10^{-3}	1.3×10^{-3}	1.2×10^{-3}	5.0×10^{-4}	6.9×10^{-5}	6.6×10^{-5}
Dust[j]	7.2×10^{-3}	7.2×10^{-3}	6.2×10^{-3}	6.2×10^{-3}	6.7×10^{-3}	3.0×10^{-3}	2.2×10^{-3}	1.2×10^{-3}	7.1×10^{-5}	7.4×10^{-5}
Total intake[k] (mg/kg bw/day)	3.5×10^{-2}	1.4×10^{-2}	1.7	1.7	3.6	3.6	4.1	4.1	2.1	2.3

Abbreviations: N/A, not applicable

[a] It is assumed that no soil ingestion occurs due to typical caregiver practices.
[b] Human milk-fed infants are assumed to consume solely human milk for six months. Human milk--fed infants 0 to 5 months old are assumed to consume 744 mL human milk per day, and human milk is assumed to be the only dietary source for infants under 6 months (Health Canada 2018). In the absence of Canadian human milk data, an arithmetic mean concentration of 0.240 µg/mL was calculated based on data from the scientific literature (Anderson 1992; Amarasiriwardena et al. 1997). As no information is available to suggest which of these studies is most representative of the typical range of titanium concentrations in the milk of Canadian women, the arithmetic mean concentration reported over studies in the US was used to estimate exposure to titanium from human milk in Canada. Infants 6 to 11 months old are assumed to consume 632 mL of human milk per day, in addition to some solid foods (Health Canada 2018).
[c] Exclusively formula-fed infants 0 to 5 months old assumed to consume 826 mL of infant formula per day, and formula is assumed to be the only dietary source for infants under 6 months (Health Canada 2018). Concentration of titanium in infant formula is assumed to be 48 µg/L, based on the measured concentration of 0.32 mg Ti/kg and a dilution of 9 g per 60 mL of water (CFIA 2020; Mead Johnson & Company, LLC 2020a, 2020b). Formula-fed infants 6 to 11 months old are assumed to consume 764 mL of formula per day (Health Canada 2018). Drinking water is used to reconstitute formula and therefore infants 0 to 5 months and 6 to 11 months are assumed to consume 826 mL and 764 mL of drinking water per day, respectively.
[d] Intake estimated using median 24-hour outdoor air sample $PM_{2.5}$ of 2.57×10^{-3} µg/m^3 (n=447) measured in Windsor, Ontario (Rasmussen 2017). Canadians are assumed to spend 3 hours outdoors each day (Health Canada 1998).
[e] Intake estimated using median 24-hour indoor air sample $PM_{2.5}$ of 1.42×10^{-3} µg/m^3 (n=437) measured in Windsor, Ontario (Rasmussen 2017). Canadians are assumed to spend 21 hours indoors each day (Health Canada 1998).
[f] Intake estimated using detection limit for titanium in drinking water from national drinking water survey of 5 µg/L (n=97). The concentration of titanium was assumed to be equal to the detection limit (5 µg/L) for all samples of water from the drinking water distribution system where titanium was not detected at or above the detection limit (Tugulea 2016).
[g] For Infants 0 to 5 months of age dietary intake was estimated as mentioned in footnotes b and c. For those 6 months and above, dietary exposure to titanium was sourced from EFSA's re-evaluation of titanium dioxide (E171) as a food additive (EFSA 2021). Intake estimates were derived from food consumption data from 40 surveys in 23 European countries and the mean reported use levels provided by industry or analytical data from European member states. When age groups were not comparable, the highest estimate was taken from the applicable age groups; details in Table A-3.
[h] For the purposes of this exposure assessment, dietary intakes generated by EFSA using the upper mean exposure value from the refined non-brand-loyal consumer scenario are presented (EFSA 2021). While there are foods that are not captured in the EFSA assessment that may contain titanium from background levels in the environment, foods on the Canadian market, including those that are permitted to contain titanium-containing food additives, generally report levels of titanium that are orders of magnitude lower relative to those employed in the EFSA assessment. Therefore, the EFSA exposure estimates are considered to be conservative as dietary exposures for the general Canadian population are, overall, expected to be lower (personal communication, email from the FD, Health Canada, to the ESRAB, Health Canada, dated April 20, 2021; unreferenced).
[i] Intake estimated on the median titanium concentration of 3 070 mg/kg in soil from Ontario soil range (Ontario [modified 2015]). Titanium bioaccesibility factor from soil was not applied to the estimated intake as bioaccessibility was assumed to be equal to oral bioavailability.
[j] Intake estimated using the median total titanium concentration of 2 100 µg/g measured in homes in Windsor, Ontario (n=1025) (Rasmussen 2017). Titanium bioaccesibility factor from dust was not applied to the estimated intake as bioaccessibility was assumed to be equal to oral bioavailability.

Appendix B. Inhalation exposure estimates of titanium dioxide from use of products available to consumers

Exposure estimates were derived for multiple age groups; however, only estimates for the age group with the highest exposure estimate are presented here. Exposure estimates were derived using the highest concentration (weight fraction) of titanium found per product type or scenario, unless otherwise noted. The concentration of titanium in products available to consumers was obtained through information notified to Health Canada under the Cosmetic Notification System, the internal SDS Search Tool (Health Canada 2019), the internal DPD [modified 2022], the LNHPD [modified 2022] and websites as described in section 5.2.2.

Product amount, retention factor and frequency of use in self-care product estimates were assumed from internal defaults, unless otherwise noted (Health Canada 2020a). The values used for product amount, exposure frequency (that is, frequency of use) and retention factors were developed through a process established for CMP assessments (Health Canada 2020a). This process includes a review of available data on product amount, frequency of use and retention factors of self-care products for comprehensiveness of the study or survey, the relevance of the data collected, and the type of information collected. The highest central tendency value from the studies with the highest quality rating is selected for use in CMP assessments, and underlying studies are cited.

Default inputs from ConsExpo Web application and associated fact sheets (RIVM 2006, 2007,2018, 2022) were used to estimate exposure from spray products unless otherwise noted in Table B-1 below. Exposure from the use of powder self-care products was estimated based on data from exposure studies as described in section 5.2.2. Air concentrations generated for pouring of powder were estimated based on unit exposure values from the US EPA PHED cited in Science Review of the AEATF II solid pour (Powder & Granule) Human Exposure Monitoring Study (US EPA 2016). Product amounts and exposure frequency of poured powders were derived from internal defaults, or ConsExpo factsheets (RIVM 2018, 2022).

Table B-1. Exposure models and factors for estimating air concentrations from the use of products available to consumers

Product	Exposure factors	Exposure (mg/m^3)
Self-care, leg foundation spray (cosmetic) Sentinel product covering aerosol body moisturizer (cosmetic),	From factsheet “Cosmetics; Deodorant cosmetics; Deodorant spray” (RIVM 2006) Scenario “Application” Exposure model “Exposure to spray spraying” (ConsExpo Web 2020) Age group: Adult 19+	Event air concentration: 0.8 mg/m^3 Mean daily air concentration: 2.8×10^{-3} mg/m^3

Product	Exposure factors	Exposure (mg/m^3)
aerosol sunless tanning product (cosmetic), aerosol body makeup (cosmetic), aerosol face makeup (cosmetic), aerosol fragrance (cosmetic), pump body spray (cosmetic), hair spray (cosmetic), nail polish spray (cosmetic), and sunscreen spray (NPD–NMI)	Concentration: 6% Ti (10% TiO_2) Exposure frequency: 1/day[a] Product amount: 1.8 g[b] Spray duration: 0.067 min[c] Exposure duration: 5 min Room volume: 10 m^3 Room height: 2.5 m Ventilation rate: 2 per hour Mass generation rate: 0.45 g/s Airborne fraction: 0.15[d] Density non-volatile: 1.8 g/cm^3 Aerosol diameter distribution type: Log-normal Median diameter: 8.3 µm Arithmetic coefficient of variation: 0.84 µm Inhalation cut-off diameter: 10 µm[e] Spraying towards person: No[f] Mean daily air concentration (mg/m^3) = Event air concentration (mg/m^3) x [exposure duration (min) x exposure frequency (/day) / 1440 min/day]	
Self-care, temporary hair colour spray (cosmetic)	From factsheet “Cosmetics; Hair care cosmetics; hair spray” Scenario “Application” (RIVM 2006) Exposure model “Exposure to hair dye spray – spraying” (ConsExpo Web 2020) Age group: Adult 19+ Concentration: 14.4% Ti (24% TiO_2) Exposure frequency: 0.019/day (=7/year) Product amount: 2.58 g Spray duration: 0.108 min[c] Exposure duration: 5 min Room volume: 10 m^3 Room height: 2.5 m Ventilation rate: 2 per hour Cloud volume: 0.0625 m^3 Mass generation rate: 0.4 g/s Airborne fraction: 0.15[g] Density non-volatile: 1.5 g/cm^3 Aerosol diameter distribution type: Log-normal Median diameter: 46.5 µm Arithmetic coefficient of variation: 2.1 µm Inhalation cut-off diameter: 10 µm[e]	Event air concentration: 0.9 mg/m^3 4 hour average air concentration: 1.9×10^{-2} mg/m^3 Mean daily air concentration: 5.9×10^{-5} mg/m^3

Product	Exposure factors	Exposure (mg/m^3)
	Spraying towards person: Yes 4 hour average air concentration (mg/m^3) = Event air concentration (mg/m^3) x [exposure duration (min) / 240 min] Mean daily air concentration (mg/m^3) = Event air concentration (mg/m^3) x [exposure duration (min) x exposure frequency (/day) / 1440 min/day]	
Self-care, face makeup (loose powder) (cosmetic) Sentinel scenario covering powdered deodorant (cosmetic), powdered body moisturizer (cosmetic), powdered body makeup (cosmetic), other loose powdered makeup products (for example, blush, eyeshadow) (cosmetic), powdered face cleanser (cosmetic) and face makeup with SPF (NHP–NMI)	Algorithm: Titanium air concentration per event (CA) = average talc study concentration × maximum Ti concentration in product Average talc study concentration: 1.36 mg/m^3 Concentration: 60% Ti (100% TiO_2) Exposure duration: 5 min[h] Exposure frequency: 1/day Mean daily air concentration (mg/m^3) = Event air concentration (mg/m^3) x [exposure duration (min) x exposure frequency (/day) / 1440 min/day]	Event air concentration: 0.82 mg/m^3 Mean daily air concentration: 2.8×10^{-3} mg/m^3
Self-care, pouring powdered bath product (cosmetic) Sentinel product covering pouring of hair bleaching powder	Algorithm: 8-hr TWA air concentration (mg/m^3) = unit exposure (8-hr TWA mg/m^3/lb ai handled) x product amount (g) x concentration Ti (%)/100 x conversion factor (1 lb/453.6 g) Unit exposure (8-hr TWA): 0.0078 mg/m^3/lb ai handled Product amount: 19 g Exposure frequency: 0.285/day (=104/year) Concentration: 60% Ti (100% TiO_2)	8-hr TWA air concentration: 2.0×10^{-4} mg/m^3 Mean daily air concentration: 1.9×10^{-5} mg/m^3

Product	Exposure factors	Exposure (mg/m^3)
	Mean daily air concentration (mg/m^3) = 8-hr TWA air concentration (mg/m^3) x (8 hours / 24 hours/day) x exposure frequency (/day)	
Cleaning product, Spray disinfectant (NPD–NMI)	From factsheet "Cleaning and Washing; All-purpose cleaners; all-purpose cleaning spray" (RIVM 2018) Scenario "Application – spraying (non-volatile substances" Exposure model "Exposure to spray – spraying" (ConsExpo Web 2020) Age group: Adult 19+ Concentration: 1.2% Ti (2% TiO_2) Exposure frequency: 1/day (=365/year) Product amount: 22 g Spray duration: 0.23 min[c] Exposure duration: 60 min Room volume: 15 m^3 Room height: 2.5 m Ventilation rate: 2.5 per hour Inhalation rate: 25 L/min Mass generation rate: 1.6 g/s Airborne fraction: 0.006 Density non-volatile: 1 g/cm^3 Aerosol diameter distribution type: Log-normal Median diameter: 2.4 µm Arithmetic coefficient of variation: 0.37 Inhalation cut-off diameter: 10 µm[e] Spraying towards person: No Mean daily air concentration (mg/m^3) = Event air concentration (mg/m^3) x [exposure duration (min) x exposure frequency (/day) / 1440 min/day]	Event air concentration: 3.6×10^{-2} mg/m^3 Mean daily air concentration: 1.5×10^{-3} mg/m^3
Cleaning product, pouring powdered dish detergent	Algorithm: 8-hr TWA air concentration (mg/m^3) = unit exposure (8-hr TWA mg/m^3/lb ai handled) x product amount (g) x concentration Ti (%)/100 x conversion factor (1 lb/453.6 g) Unit exposure (8-hr TWA): 0.0078 mg/m^3/lb ai handled Product amount: 46 g	8-hr TWA air concentration: 4.7×10^{-6} mg/m^3 Mean daily air concentration: 1.6×10^{-6} mg/m^3

Product	Exposure factors	Exposure (mg/m^3)
	Exposure frequency: 1/day (=365/year) Concentration: 0.6% Ti (1% TiO_2) Mean daily air concentration (mg/m^3) = 8-hr TWA air concentration (mg/m^3) x (8 hours / 24 hours/day) x exposure frequency (/day)	
Paints and coatings, aerosol spray paint can Sentinel scenario covering application of wall paint using pneumatic sprayer, aerosol rust enamel spray, aerosol adhesives and sealants, spray ceiling and wall texture, spray floor coatings and aerosol waterproofing spray	From factsheet "Paint products; Spray painting; spray can" (RIVM 2007) Scenario "Application" Exposure model "Exposure to spray – spraying" (ConsExpo Web 2020) Age group: Adult 19+ Concentration: 15% Ti (25% TiO_2) Exposure frequency: 0.0055/day (=2/year) Product amount: 340 g (adjusted for standard size of can) Mass generation rate: 0.45 g/s Spray duration: 13 min[c] Exposure duration: 20 min Room volume: 90 m^3 (adjusted for 2 car garage) Room height: 2.25 m Ventilation rate: 1.5 per hour Airborne fraction: 0.7 Density non volatile: 1.5 g/cm^3 Inhalation cut-off diameter: 10 µm[e] Aerosol diameter distribution type: Log-normal Median diameter: 15.1 µm Arithmetic coefficient of variation: 1.2 Spraying towards person: No 4 hour average air concentration (mg/m^3) = Event air concentration (mg/m^3) x [exposure duration (min) / 240 min] Mean daily air concentration (mg/m^3) = Event air concentration (mg/m^3) x [exposure duration (min) x exposure frequency (/day) / 1440 min/day]	Event air concentration: 59 mg/m^3 4 hour average air concentration: 4.9 mg/m^3 Mean daily air concentration: 4.5×10^{-3} mg/m^3
DIY product, pouring powdered tile grout	Algorithm: 8-hr TWA air concentration (mg/m^3) = unit exposure (8-hr TWA mg/m^3/lb ai handled) x product amount (g) x concentration Ti (%)/100 x conversion factor (1 lb/453.6 g)	8-hr TWA air concentration: 2.6×10^{-2} mg/m^3

Product	Exposure factors	Exposure (mg/m^3)
	Unit exposure (8-hr TWA): 0.0078 mg/m^3/lb ai handled Product amount: 25 000 g Exposure frequency: 0.00137 /day (=1 / 2 years) Concentration: 6% Ti (10% TiO_2) 4 hour average air concentration = 8-hr TWA air concentration (mg/m^3) x (8 hours/4 hours) Mean daily air concentration (mg/m^3) = 8-hr TWA air concentration (mg/m^3) x (8 hours / 24 hours/day) x exposure frequency (/day)	4 hour average air concentration: 5.2×10^{-2} mg/m^3 Mean daily air concentration: 1.2×10^{-5} mg/m^3

Abbreviations: DIY, do it yourself; NHP, natural health product; NMI, non-medicinal ingredient; TiO_2, titanium dioxide; NPD, non-prescription drug; SPF, sun protection factor

[a] Frequency of use assumed to be daily for body makeup (professional judgement).

[b] Product amount (5.2 g) adjusted by the ratio of legs surface area (5 970 cm^2)/total body - head surface (17 530 cm^2) area as the product is intended for use on legs (Health Canada 2020a).

[c] Default spray duration adjusted to account for adjusted product amount. Spray duration (min) = total product amount (g) / mass generation (g/s) x (1 min/60 s)

[d] Airborne fraction modified to 0.15 to account for 85% of deodorant assumed to land on skin (RIVM 2006).

[e] ConsExpo default for inhalation cut-off diameter is 15 µm; this has been refined to a cut-off of 10 µm for inhalable particles (Health Canada).

[f] Assume the product is sprayed away from the person as it is a product intended for use on the legs.

[g] Airborne fraction modified to 0.15 to account for 85% of hair spray assumed to land on head (RIVM 2006).

[h] Exposure time for powder face makeup is 5 minutes considering the duration of particle cloud, study sampling duration, formation of secondary exposure clouds and median time spent in the bathroom following a shower or bath (RIVM 2007; US EPA 2011; ECCC, HC 2021).

Appendix C. PBPK model for titanium and BE derivation

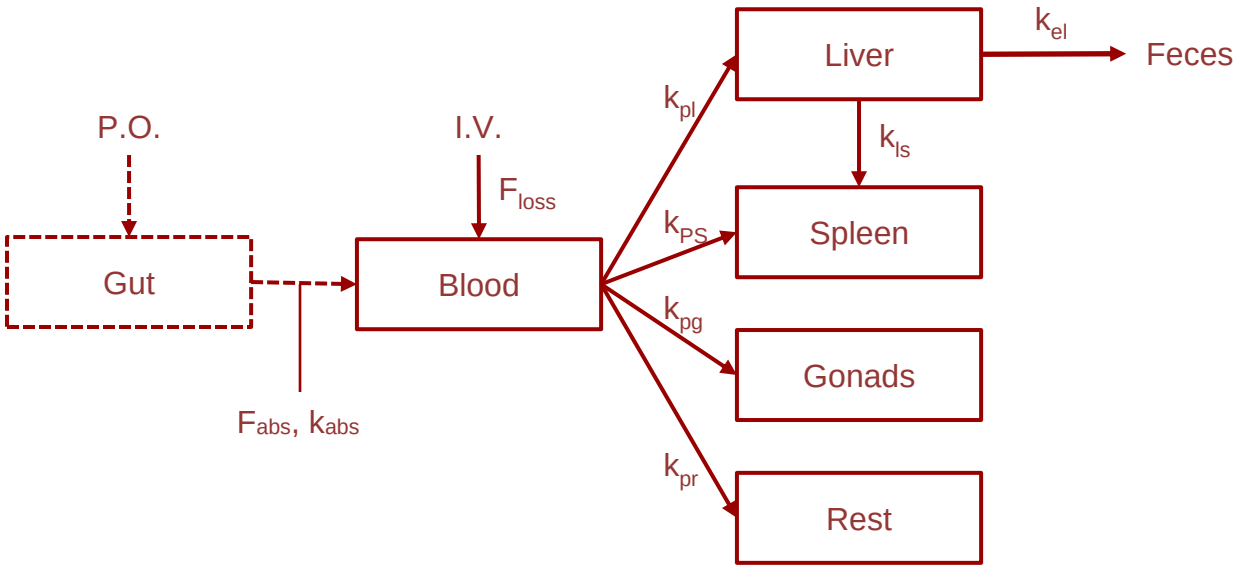

Figure C-1. PBPK model for titanium and titanium dioxide

Figure C-1. Pharmacokinetic model for titanium and titanium dioxide. Abbreviations: P.O., per oral; I.V., intravenous; F_{abs}, fraction absorbed; k_{abs}, kinetic rate of absorption; k_p's, kinetic rates from the blood to the liver (l), spleen (s), gonads (g), or rest (r), or from the liver to spleen (ls) and for elimination from the liver to feces (el) (from Ramoju et al. 2020).

Long description of the figure: Figure C-1 is a schematic of the six-compartment PBPK model of titanium. The figure includes six compartments (gut, blood, liver, spleen, gonads, and the rest) and an excretion pathway (feces). Oral doses of titanium are presented by an arrow from the stomach into the blood compartment, whereas I.V. doses of titanium are represented by an arrow directly to the blood compartment. From blood compartment, titanium partitioning to liver, spleen, gonads and the rest of the body. The fraction absorbed from gut to blood compartment is shown alongside of the arrow from gut to blood compartment. The kinetic rates are presented alongside the arrows directing from gut to blood, blood to each compartment, liver to spleen and liver to excretion pathway (that is, feces).

Table C-1. Derivation of BE for the NOAEL from EOGRT study (REACH [modified 2022]) using kinetic parameters described in the PBPK model by Ramoju et al. (2020).

BE derivation step[a]	Male Rats	Female Rats
POD (NOAEL), external dose (mg Ti/kg-bw/day)	623	623

BE derivation step[a]	Male Rats	Female Rats
BE-POD (NOAEL), steady-state blood concentration (mg Ti/L blood)	2.15	1.61
UF (inter-species, toxicodynamic)	2.5	2.5
BE-POD (mg Ti/L blood)	0.86	0.65
UF (intra-species variation)	10	10
BE, Blood concentration (mg Ti/L blood)	0.0860	0.0646
BE, Blood concentration (µg Ti/L blood)[b]	86	65

Abbreviations: BE, bioequivalent; L, litre; mg, milligram; NOAEL, no observed adverse effect level; POD, point of departure; Ti, titanium; UF, uncertainty factor

[a] Model code for titanium pharmacokinetics in rat after oral administration (recoded in Berkeley Madonna; an original model by Heringa et al. 2016) was obtained from the supplementary data to Ramoju et al. (2020).

[b] Multiplied by 1 000 to convert from mg/L to µg/L, rounded to 2 significant figures.